Asymmetric Organocatalysis in Complex Target Synthesis: Progress Towards the Total Synthesis of Diazonamide A

Thesis by

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I know of no more encouraging fact than the unquestionable ability of a man to elevate his life by a conscious endeavor.

~H. D. Thoreau, 1854

For my grandfathers

Acknowledgements

I feel incredibly fortunate and proud to have been in the MacMillan group for the past five years. Witnessing the development of so much exciting chemistry and working alongside such an intelligent and dedicated group of people has made for an incredible education. I am a better person and a better scientist because of my time here, and I am truly grateful for it.

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Lastly, and most importantly, I want to thank my wife, Sandy. Getting a Ph.D. is a long, hard road and I doubt very honestly that I would have made it through with her support and encouragement. She has sacrificed a great deal in order for me to finish my degree, and for this I am grateful. She is my best friend and partner, and my better half in every respect.

Abstract

Progress towards the total synthesis of the marine natural product diazonamide A is described. The synthesis was conceived around an iminium-catalyzed alkylation/cyclization cascade that stereoselectively installs the central C(10) quaternary carbon stereocenter and the complete furanoindoline core of the natural product in an asymmetric, organocatalytic manner. The manner in which this idea was brought to bear is illustrated, with the remainder of the work focused on devising and executing strategies toward the synthesis of the two twelve-membered macrocycles of the target structure. Considerable efforts were made in this regard, and highlights include execution of a Witkop photo-annulation, development of a novel and highly selective magnesium-mediated macroaldolization reaction to close a thirteen-membered ring, a Suzuki biaryl macrocyclization, an unusual oxidative ring contraction, and the development of a new DAST-mediated method for the synthesis of 4-acyl oxazoles. Five distinct approaches towards the endgame of the synthesis are described. In all cases these approaches came only a single synthetic operation from the assured completion of the natural product, but none proved ultimately viable.

Also described is work focused on replacing a late-stage auxiliary-based aldol reaction in a previously completed MacMillan group synthesis of the macrolide antibiotic erythronolide B, with a substrate-controlled, diastereoselective variant. The overarching synthetic strategy and forward synthesis will be described along with a detailed discussion of the aforementioned, late stage aldol reaction to install the C(1)-C(2) portion of the seco acid.

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Abbreviations

3-D	three-dimensional
Ac	acetate
Ac_2O	acetic anhydride
AgTFA	silver(I) trifluoroacetate
AIBN	2,2-azobisisobutyronitrile
AM-1	Austin model 1
ax	axial
Bn	benzyl
BnBr	benzyl bromide
Boc	*tert*-butyl carbamate
Boc_2O	di-*tert*-butyl dicarbonate
BOM	benzyloxy methyl
BOPCl	bis(2-oxo-3-oxazolidinyl)phosphinic chloride
$Bpin_2$	bis(pinacolato)diboron
BzF	benzoyl fluoride
CAM	ceric ammoniun molybdate
CAN	ceric ammoniun nitrate
Cbz	benzyl carbamate
CbzCl	benzyl chloroformate
CSA	camphor sulfonic acid
CbzSu	*N*-(benzyloxycarbonyloxy)succinimide
DAST	diethylaminosulfurtrifluoride
dba	dibenzylidene acetone
DBU	diazabicylcoundecene
DCE	dichloroethane
DCM	dichloromethane
DDQ	dicyano dichlror quinone
DFT	density functional theory
DIBAL-H	diisobutyl aluminum hydride
DIPEA	*N*,*N*-diisopropylethylamine
DMA	dimethylacetamide

DMAP	4-(dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
DNBA	3,5-dinitrobenzoic acid
dppf	1,1'-bis(diphenylphosphino)ferrocene
EDC	*N*-(3-dimethylaminopropyl)-N'-ethylcarbodiimide
ee	enantiomeric excess
eq	equatorial
ESI	electrospray ionization
FAB	fast-atom bombardment
Fmoc	9-fluorenylmethoxycarbonyl
GTP	guanosine 5′-triphosphate
HATU	*O*-(7-azabenzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate
HeLa	Henrietta Lacks cervical cancer cell line
hex	hexanes
HOBT	1-hydroxybenzotriazole
HRMS	high-resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
hν	photo irradiation
Hz	Hertz
IBX	iodosobenzoic acid
IC_{50}	concentration necessary for 50% inhibition
IPA	isopropyl alcohol
IR	infrared
Kcal	kilocalorie
KHMDS	potassum hexamethyldisilazide
LA	Lewis acid
LiHMDS	lithium hexamethyldisilazide
LUMO	lowest unoccupied molecular orbital
Mg	milligram
MHz	megahertz

MM3	molecular mechanics 3 force field
MOM	methoxymethyl
mRNA	messenger ribonucleic acid
NCS	*N*-chlorosuccinimide
nM	nanomolar
nm	nanometer
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
Ns	nosyl
OAT	ornithine acyl transferase
PFPA	pentafluoropropionic acid
Piv	pivoate
PMB	*para*-methoxy benzyl
PMBCl	*para*-methoxy benzyl chloride
PMP	*para*-methoxy phenyl
ppm	parts per million
***p*-TSA**	*para*-toluene sulfonic acid
PyBrop	bromotripyrrolidinophosphonium hexafluorophosphate
RNA	ribonucleic acid
siRNA	small interfering ribonucleic acid
S-Phos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
TASF	tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TBTU	*O*-(benzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium tetrafluoroborate
TCA	trichloroacetic acid
Teoc	2-(trimethylsilyl)ethyl carbonate
Tf	triflate
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anyhydride
THF	tetrahydrofuran

TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
$TMSCHN_2$	trimethylsilyldiazomethane
TMSCl	trimethylsilyl chloride
TMSE	trimethylsilylethyl
TPAP	tetrapropyl ammonium perruthenate
TTMS	tris(trimethylsilyl)silane
UV	ultraviolet

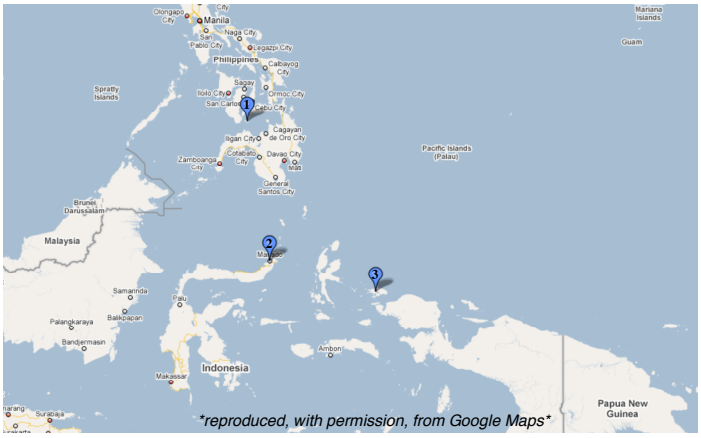
Chapter 1

Isolation, Structural Elucidation, and Biological Activity of the Diazonamides

I. Isolation

The diazonamides are a structurally unique class of secondary metabolites produced by colonial marine ascidians of the genus *Diazona.* The first members of the class were reported in 1991 when Fenical and coworkers isolated diazonamides A (**1**) and B (**2**) from the methanol extracts a colony of *Diazona angulata* harvested in the waters off Siquijor Island in the Philippines.[1] Subsequently, in early 2008, Reyes and coworkers reported the isolation of diazonamides C, D, and E (**3**–**5**) from an unspecified *Diazona* species found in Indonesian waters near Manado and Raja Ampat, roughly 500 miles south and 775 miles southeast, respectively, of the original isolation site (Figure 1).[2]

Figure 1: Isolation sites of the diazonamides in the south seas



Legend: (1) Sijiquor Island, Phillipines. (2) Manado, Indonesia. (3) Raja Ampat, Indonesia.

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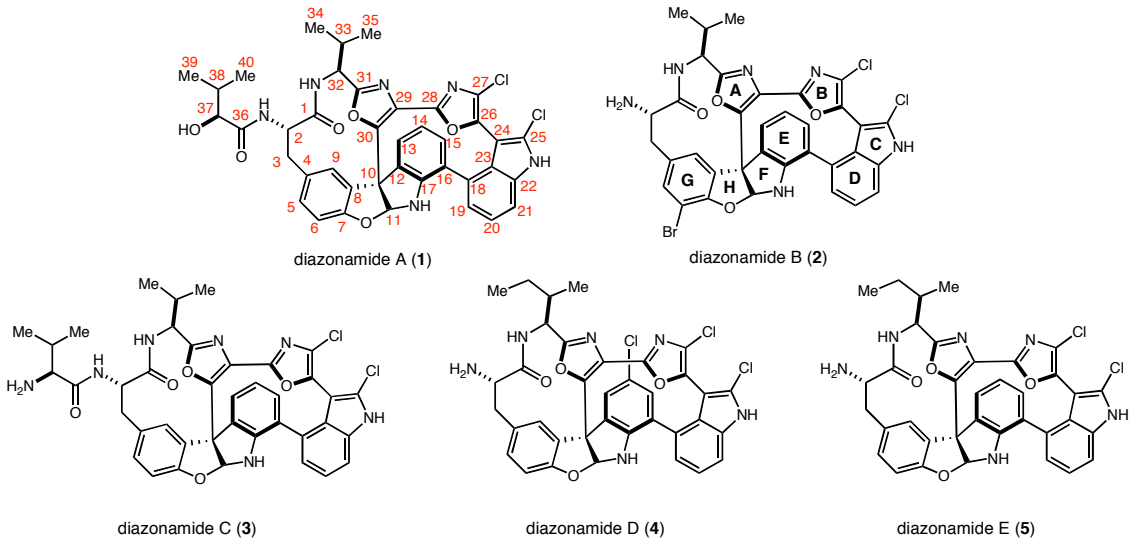
[1] Lindquist, N.; Fenical, W.; Van Duyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1991**, *113*, 2303–2304.

[2] Fernandez, R.; Martin, M. J.; Rodriguez-Acebes, R.; Reyes, F.; Francesch, A.; Cuevas, C. *Tetrahedron Lett.* **2008**, *49*, 2282–2285.

Figure 2: The diazonamides



The compact, polycyclic structures of the diazonamides are wholly unprecedented in the natural product literature and the relationships between their dominant structural features are distinctive and complex (Figure 2). All of the diazonamides consist of two conjoined twelve-membered macrocycles, effectively dividing the molecule into two discrete hemispheres. In each member, the right-hand macrocycle contains only a single sp^3 carbon and all of its four constituent aromatic ring systems (A-B-CD-E) lie out of conjugation with one another, creating an impressive cyclophane-type substructure. Moreover, within the cyclophane, the B-ring oxazole exists as a single atropisomer along the A-B-C axis. The left-hand ring is a highly strained twelve-membered lactam containing two *ansa*-bridged aromatic rings and three stereogenic centers. These two large ring systems are fused together through a central triaryl-substituted quaternary carbon stereocenter at C(10) imbedded in a highly unusual tetracyclic furanoindoline core (E-F-G-H). Taken together, these features result in an extraordinarily compact, rigid, and exotic topography whose inner atoms possess almost no rotational degrees of freedom. These molecules differ from one another only in the pattern of halogenation on the

periphery of the aromatic rings, the presence and identity of the C(36)–C(40) side chain, and the inclusion of either a valine or isoleucine side chain appended to C(32).

These impressive structural attributes, together with potent anti-cancer activity (*vide supra*) and the lack of an abundant and renewable natural source, make the diazonamides exceptionally attractive targets for *de novo* synthesis. In fact, few molecules in recent history have generated such intense and sustained synthetic interest.[3] This thesis will endeavor to catalogue the fascinating history of the diazonamides from a synthetic chemist's point of view, with an attendant emphasis on their structural features as they relate to both the biological function of these molecules and the ideas advanced in regard to their construction.

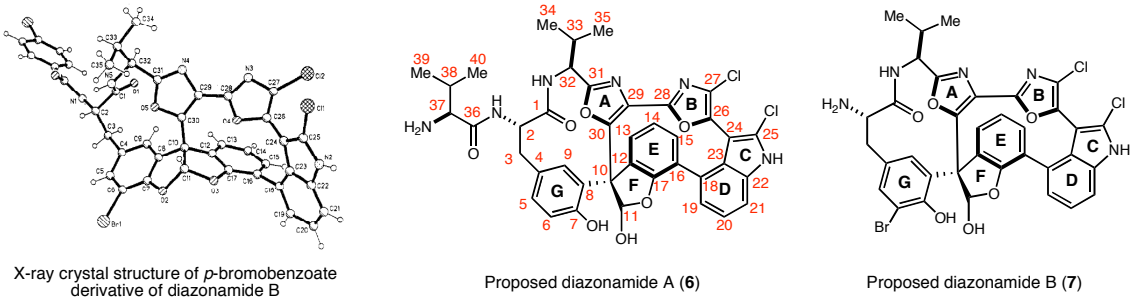
II. Original Structural Proposal for Diazonamides A and B

Perhaps the most famous chapter in the diazonamide story revolves around the fact that the structures of diazonamide A and B were notoriously misassigned as **6** and **7**, respectively, in Fenical and Clardy's original report (Figure 3). Even though 54 mg of diazonamide A and 132 mg of diazonamide B were collected in the original 1991 isolation, the large proportion of heteroatoms and unprotonated carbons precluded a complete and unambiguous NMR structural determination. Even though all of the constituent spin systems could be unambiguously identified, the way in which they were bonded together could not be determined with certainty. However, this difficulty was

[3] For a recent, comprehensive review of the synthetic efforts toward **1**, see: Lachia, M.; Moody, C. J. *Nat. Prod. Rep.* **2008**, *25*, 227–253.

overcome when the isolation chemists were successful in solving an X-ray crystal structure of a *p*-bromobenzoate derivative of diazonamide B (Figure 3).[4,5]

Figure 3: Originally proposed structures and accepted labeling for nominal diazonamide A



X-ray crystal structure of *p*-bromobenzoate derivative of diazonamide B

Proposed diazonamide A (**6**)

Proposed diazonamide B (**7**)

The X-ray data exhibits many of the features of **1**–**5** discussed above, with one crucial and notable exception. The diffraction pattern was unable to resolve the positions of the protons associated with the heteroatoms attached to C(11), leading Fenical and Clardy to assign both atoms as oxygen. However, this assignment was inconsistent with the observation of an exchangeable proton resonance at δ 7.36 possessing a 3.5 Hz coupling to the C(11) proton at δ 6.46 in the ^{1}H NMR. To account for this, the isolation chemists proposed that the crystal structure connectivity corresponds to a dehydrated and cyclized form of diazonamide B, and that E-F-G ring system actually existed as an open hemiacetal form in the natural product, as shown in **7**. Loss of water was proposed to occur during mass spectrometry to reconcile the observed molecular ions with the proposed molecular formulas. Based on this rationale, and the assumption that the diazonamide A side chain was valine, Fenical put forward structures **6** and **7** as being the natural forms of diazonamide A and diazonamide B, respectively (Figure 3).

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[4] Diazonamide A was assigned by analogy to the crystal structure of diazonamide B, based on the similarity of the NMR data. The differentiating side chain was assumed to be L-valine.

[5] The X-ray structure in Figure 3 was reproduced with permission from the ACS. Originally published in Lindquist, N.; Fenical, W.; Van Duyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1991**, *113*, 2303–2304.

III. A Revised Structural Proposal

Spurred by this initial report, more than a dozen synthetic research groups began to investigate and report synthetic routes to **6** in the early and mid 1990s. Yet, it took nearly a full decade until Harran and coworkers at University of Texas–Southwestern Medical Center finally succeeded in reporting a completed synthesis of **6** in late 2001.[6] However, the excitement around this impressive synthetic achievement was quickly tempered by the fact that the NMR spectral data for synthetic **6** did not match that reported for the natural product in the isolation paper. Moreover, synthetic **6** proved to be unstable to routine handling and purification protocols. In light of these findings, Harran proposed that structure **6** originally put forward by Fenical and Clardy was incorrectly assigned, and on the basis of the following propositions, put forward a new proposal for the true structure of diazonamide A.

It was known that an acid digest of the natural product produces no valine.[7] Moreover, the C(36)-methine resonance is observed at δ 76.9 ppm in the ^{13}C NMR, an anomalously high shift for a valine freebase. These facts taken together argue strongly against the proposal that valine constitutes the C(36)–C(40) side chain. Rather, Harran postulated that that this fragment was much more likely to be the corresponding α-hydroxy acid.

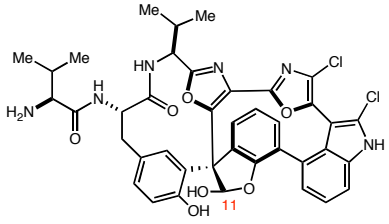
Yet, to reconcile the molecular formula with this NH_2 to OH substitution, a compensatory O to NH transposition in **6** was required. Realizing this meant that Fenical's crystal structure had been misassigned, Harran exhaustively re-analyzed the original crystal data set, as well as a series of $^{1}H/^{13}C$ and $^{1}H/^{15}N$ HSQC NMR

[6] Li, J.; Jeong, S.; Esser, L.; Harran, P. G. *Angew. Chem. Int. Ed.* **2001**, *40*, 4765–4769.

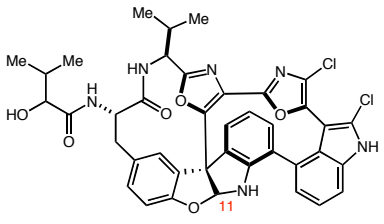
[7] Lindquist, N. *Ph.D. Thesis*, University of California, San Diego, 1989.

experiments on a natural sample of diazonamide A. Harran convincingly demonstrated that one of the heteroatoms attached to C(11) was nitrogen, and that the true structure of the diazonamide A possessed a closed form of the tetracyclic aminal. This prompted him to put forth **1** as the likely structure of diazonamide A (Figure 4). [8]

Figure 4: Originally proposed and revised structures of diazonamide A



Proposed diazonamide A (**6**)



Revised diazonamide A (**1**)

If correct, this structural hypothesis would possess one particularly pleasing and intuitive feature that was notably absent in its predecessor, **6**. Specifically, this revision suggests a very clear and compelling hypothesis for the biosynthetic origin of the diazonamides (Figure 4). While the majority of the structure of **6** is clearly derived from naturally occurring amino acid residues, the biosynthetic origin of the central dihydrobenzofuran was far from obvious. Yet, the indoline moiety of **1** is almost certainly derived from an oxidized congener of the amino acid tryptophan. As such, Harran proposed the biosynthetic origins of diazonamide A to be based on the oxidative cyclizations of a hydroxy acid conjugated-tertrapeptide, as shown in Figure 5.

Confirmation of this hypothesis came in 2002–2003 through a series of completed total syntheses of **6**, all of which will be discussed in detail in the following chapter.

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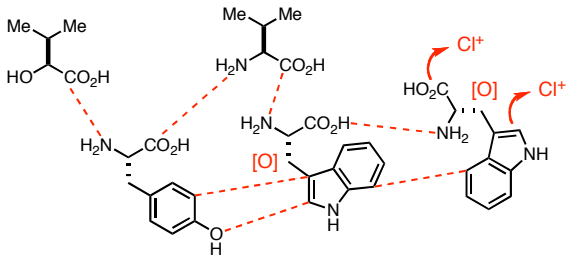
[8] Li, J.; Burgett, A. W. G.; Esser, L.; Amecuza, C.; Harran, P. G. *Angew. Chem. Int. Ed.* **2001**, *40*, 4769–4772.

Figure 5: Harran's proposed biosynthesis of diazonamide A

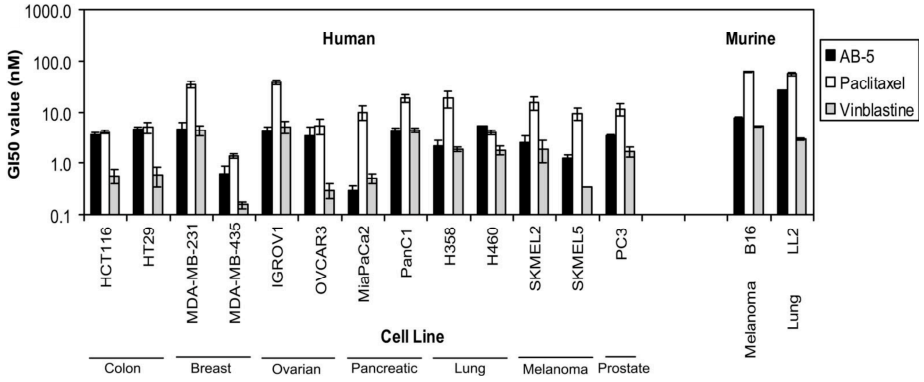


However, the collateral damage from this structural revision incurred by the synthetic community was unprecedented. With the structure of **6** now shown to be demonstrably incorrect, and substantially different from the true structure **1**, nearly all of the groups who had been so heavily invested in the synthesis of these incredibly popular targets over the past decade now found themselves with obsolete synthetic strategies. Yet, as with any such rapid change in perspective, this new structure provided attendant opportunities to develop interesting synthetic strategies toward the newer structure. Both the theme and topic for the subsequent chapters of this thesis are the numerous creative ways in which these opportunities have been made manifest.

IV. Biological Activity and Therapeutic Potential

In the original isolation paper, diazonamide A was reported to exhibit low nanomolar *in vitro* activity against HCT-116 human colon carcinoma and B-16 murine melanoma cell lines. Subsequent investigations showed that this nanomolar inhibition also extended to many other human cancers, including multiple cell lines of ovarian, breast, colon, pancreatic, melanoma, and lung cancer (Figure 6).

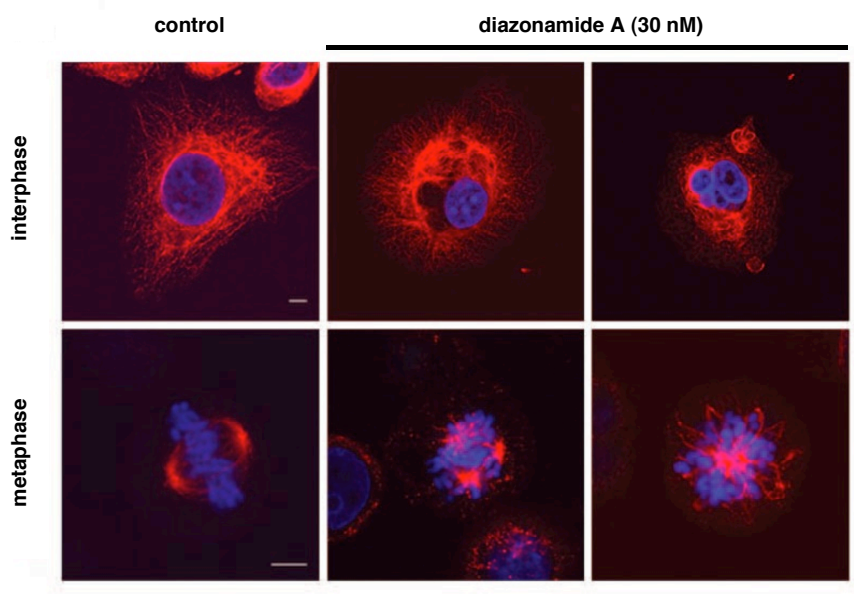
Figure 6: GI_{50} values for diazonamide A analog against a range of cancer cell lines [1,2]



[1]AB-5 is *deschloro*-diazonamide A
[2] Reproduced from Wang, G.; Shang, L.; Burgett, A. W. G.; Harran, P. G.; Wang, X. *Proc. Nat. Acad. Sci. USA* **2007**, *104*, 2068–2073

Initial investigations into the specific biological mode of action showed that diazonamide A was an antimitotic agent, arresting division at the G2/M interface of the cell cycle. Specifically, cells treated with diazonamide A and closely related synthetic analogues lacked a viable mitotic spindle (Figure 7).

Figure 7: Diazonamide-treated HeLa cells



Reproduced from Williams, N. S.; Burgett, A. W.; Atkins, A. S.; Wang, X.; Harran, P.; McKnight, S. L. *Proc. Nat. Acad. Sci. USA* **2007**, *104*, 2074–2079.

The qualitative similarity of these observations to the effects of other classical small molecule antimitotic agents, such as Taxol and the *vinca* alkaloids, led to an initial assumption that diazonamide acted as a tubulin-binding agent. Armed with this belief, researchers endeavored to identify the binding site for **1** on the protein. The Taxol-binding site was discounted by Nicolaou, who showed that **1** exhibited 2–5 nM IC_{50} values against 1A9/PTX10 cells, a strain of ovarian cancer that is resistant to treatment with Taxol due to an acquired mutation in the Taxol-binding site on β-tubulin.[9] Moreover, Cruz-Monserrate showed that **1** did not competitively inhibit the binding of vinblastine, dolastatin 10, or GTP to tubulin.[10] This led these workers to initially postulate that **1** must occupy a new and unique binding site on tubulin; one that it does not share with any other known tubulin-binding molecules. Yet, no positive evidence for such an interaction could be found.

Harran and coworkers later attempted to test the tubulin-binding hypothesis directly by carrying out binding affinity studies between purified tubulin and radio-labeled or biotinylated analogues of **1**. Surprisingly these analogues of **1** did not bind with either monomeric tubulin or microtubules *in vitro*.[11] Rather, affinity screening using biotinylated **1** revealed that ornithine acyl transferase (OAT), a well-characterized mitochondrial matrix protein, was the cellular target of diazonamide A. This was a highly unexpected finding. OAT was known to regulate flux in the urea cycle and to couple

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[9] Nicolaou, K. C.; Hao, J.; Reddy, M. V.; Rao, P. B.; Rassias, G.; Snyder, S. A.; Huang, X.; Chen, D. Y.-K.; Brenzovich, W. E.; Giuseppone, N.; Giannakakou, P.; O'Brate, A. *J. Am. Chem. Soc.* **2004**, *126*, 12897–12906.

[10] Cruz-Monserrate, Z.; Vervoort, H. C.; Bai, R.; Newman, D. J.; Howell, S. B.; Los, G.; Mullaney, J. T.; Williams, M. D.; Pettit, G. R.; Fenical, W.; Hamel, E. *Mol. Pharm.* **2003**, *63*, 1273–1280.

[11] Wang, G.; Shang, L.; Burgett, A. W. G.; Harran, P. G.; Wang, X. *Proc. Nat. Acad. Sci. USA* **2007**, *104*, 2068–2073.

proline biosynthesis to consumption of fumarate in the citric acid cycle, but it had never been implicated in cell division.[12] To address the possibility that OAT may play some hitherto unappreciated role in mitosis, siRNA strands were synthesized to block OAT synthesis in HeLa cells by selectively inactivating OAT mRNA.[11] After 48 hours the HeLa cells treated with the designer siRNAs exhibited mitotic spindle defects similar to those observed upon exposure to diazonamide A, with cells accumulating at the G2/M interface. After 72 hours, cell death was observed in the majority of the treated cells, substantiating the hypothesis that OAT is the cellular target of diazonamide A and is essential to proper mitotic function and propagation in HeLa cells.

This was a puzzling result, as it is well established that OAT-null mice and OAT-deficient humans are viable, implying that OAT is not essential in development.[13] This is hardly likely if the enzyme is a key regulator in essential cellular processes such as division. As such, Harran and coworkers boldly hypothesized that OAT may be selectively utilized as a regulatory factor in mitosis by the cancer cells that exhibit diazonamide sensitivity, but not in healthy human cells.

If true, diazonamide A would represent a novel class of antimitotic small-molecule inhibitor that has an intrinsically cancer-selective enzyme target. A corollary of this would be that if diazonamide was viable as an *in vivo* therapy, it should not exhibit any of the systemic toxicity characteristics of the classical tubulin binding antimitotics, which discriminate poorly between cancerous and healthy cells.

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[12] Seller, N. *Current Drug Targets* **2000**, *1*, 119–153.

[13] (a) Wang, T.; Lawler, A. M.; Steel, G.; Sipila, I.; Milam, A.H.; Valle, D. *Nat. Genet.* **1995**, *11*, 185–190. (b) Brody, L. C.; Mitchell, G. A.; Obie, C.; Michaud, J.; Steel, G.; Fontaine, G.; Robert, M. F.; Sipila, I.; Kaiser-Kupfer, M.; Valle, D. *J. Biol. Chem.* **1992**, *267*, 3302–3307.

To address this hypothesis, Harran and McKnight tested the hypothesis in nude mice.[14] Tumors were xenografted onto nude mice, which were then subjected to a regimen of both **1** and Taxol. **1** was shown to be just as effective *in vivo* as it was *in vitro*, causing rapid regression of tumor growth, with 44% of mice being tumor free after 100 days. Moreover, the mice treated with **1** exhibited no weight loss or loss of appetite, while Taxol-treated mice lost on average 20% of their body weight. Also, mice treated with **1** exhibited no signs of neutropenia, a major dose-limiting side effect in Taxol and vinblastine based therapies. This lack of overt toxicity, coupled with low nanomolar, broad-spectrum anti-tumor activity make **1** a truly unique and promising cancer therapy.[15]

V. Known Structure-Activity Relationships

Toward this end, structure-activity relationships for a number of diazonamide derivatives have been established, illustrating which features are crucial for biological activity. Some of the most illuminating data comes from comparing the activities of the natural isolates themselves. **1** and **3** differ only in that **1** possesses the α-hydroxy side chain at C(38) while **3** possesses an α-amino group. Yet **1** is more than 300 times more active than **3** against lung (A549), colon (HT29), and breast (MDA-MB-231) cancer cell lines.[2] Notably, all of the diazonamides lacking the C(36) side chain are much less active than **1**.[2] Thus, it is presumed that the α-hydroxy side chain is essential for potency.

Harran found that the when the α-hydroxy C(36) side chain is appended to the tetracyclic acetal derived from nominal diazonamide A (**6**), it is equipotent to **1**.[8] Thus the

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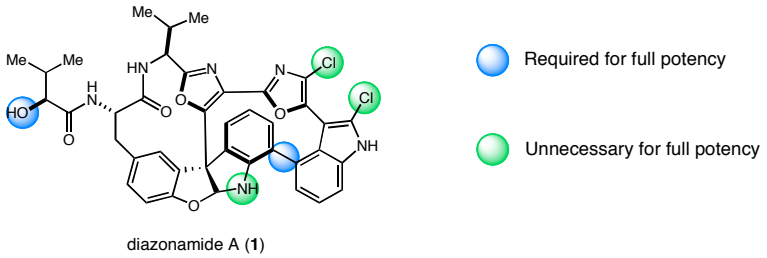
[14] Williams, N. S.; Burgett, A. W.; Atkins, A. S.; Wang, X.; Harran, P.; McKnight, S. L. *Proc. Nat. Acad. Sci. USA* **2007**, *104*, 2074–2079.

[15] Joyant Pharmaceuticals has licensed the rights to develop diazonamide A as commercial anti-cancer therapy.

identity of the left-hand heteroatom attached to C(11) is unimportant. Also, Harran found that *des*-chloro diazonamide A is equipotent to **1**, illustrating that the aryl chlorides are unnecessary for high levels of biological activity.[11] Lastly, he found that structures lacking the D-E biaryl bond were more than a 100-fold less potent than **1**.

Figure 8: Known structure-activity relationships in the diazonamide series



diazonamide A (**1**)

Taken together this knowledge can be compiled to give a fairly representative view of the structural aspects of **1** that are necessary for potent biological activity (Figure 8). Unfortunately, such an analysis does little to suggest structurally less complex analogues that have a reasonable chance of remaining highly active. But, in time, all the work invested in the diazonamides is likely to bear significant fruit. Even if the molecules themselves are never developed as viable therapeutics, the elucidation of the OAT-dependence of cell division in certain cancer cell lines is of fundamental importance. It is highly likely that a traditional small-molecule drug discovery program aimed at discovering OAT antagonists could be successfully undertaken, with the hope of developing an entire class of promising new antineoplastic therapies. In the meantime, discovering ever-better routes to **1** will facilitate the basic biological investigations of this pathway.

In closing, it should be noted that this work is a particularly striking example of the way in which synthetic chemistry, and complex target synthesis in particular, can still

be an engine for scientific discovery. The true structure of diazonamide A was arrived at on the basis of two completed total syntheses, one revealing the original structural misassignment and the other confirming the true structure. Moreover, the amount of **1** isolated from natural sources would never satisfy the demand needed to fully elucidate the mode of biological action. Despite the great difficulty associated with its synthesis, synthetic **1** and its derivatives played the crucial role in elucidating the OAT-dependent mitotic pathway, which opened up exciting new avenues for both drug discovery and fundamental oncology. Though it may be vocally and frequently disparaged for being increasingly irrelevant, this story is testament to the central role of chemical synthesis still plays in the advancement of human medicine and its associated biological sciences.

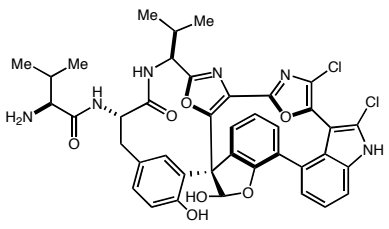
Chapter 2

Prior Efforts Toward the Synthesis of Diazonamide A

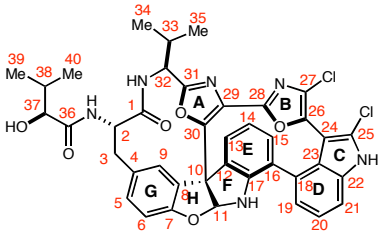
I. Introduction

Prior to the outset of the MacMillan group's synthetic investigations of diazonamide A, many approaches to the molecule and several completed syntheses had been described in the literature.[1] The successes and failures of these earlier studies provided much of the context for our own work and will frame the discussion in subsequent chapters about the unique advantages and liabilities that our asymmetric organocatalytic strategy imposes in addressing the most challenging structural features of the target. Due to the fact that this area has been often and extensively reviewed in recent years, this chapter will only discuss highlights from the one completed synthesis of the nominal structure of diazonamide A (**1**), the three completed total syntheses of true diazonamide A (**2**), and one formal synthesis of **2** that have appeared in the literature. Specifically, these brief descriptions will focus on the strategies and methods used to assemble the E-F-H-G tetracyclic core, the two twelve-membered macrocycles, and the central C(10) quaternary carbon stereocenter (Figure 1).

Figure 1: Structures, accepted carbon numbering, and ring labeling



nominal diazonamide A (**1**)



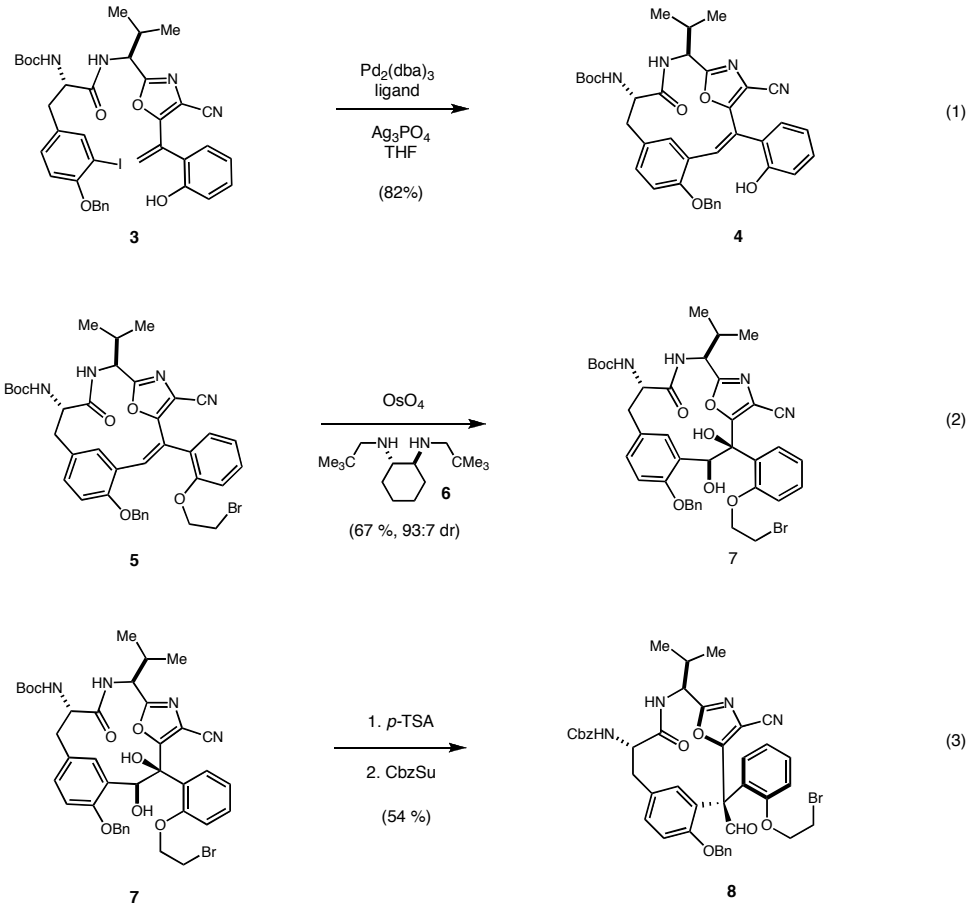
diazonamide A (**2**)

[1] For reviews on the synthetic efforts towards both the original and revised diazonamide structures, see: (a) Lachia, M.; Moody, C. J. *Nat. Prod. Rep.* **2008**, *25*, 227–253. (b) Ritter, T.; Carriera, E. M. *Angew. Chem. Int. Ed.* **2002**, *41*, 2489–2495. (c) Fuerst, D. E. *Ph.D. Thesis*, Yale University, 2004.

II. Harran's Synthesis of Nominal Diazonamide A

As described in Chapter 1, in late 2001 Harran and coworkers completed a synthesis of nominal diazonamide A (**1**) only to discover that the structure of the natural product had been misassigned in the isolation paper.[2,3] Yet, due to this work being the only successful total synthesis of **1** and in light of the large degree of structural homology between **2** and **1**, this work was highly influential in all future syntheses of **2**. Selected highlights from this work are described herein.

Scheme 1: Key steps from Harran's synthesis of nominal diazonamide A

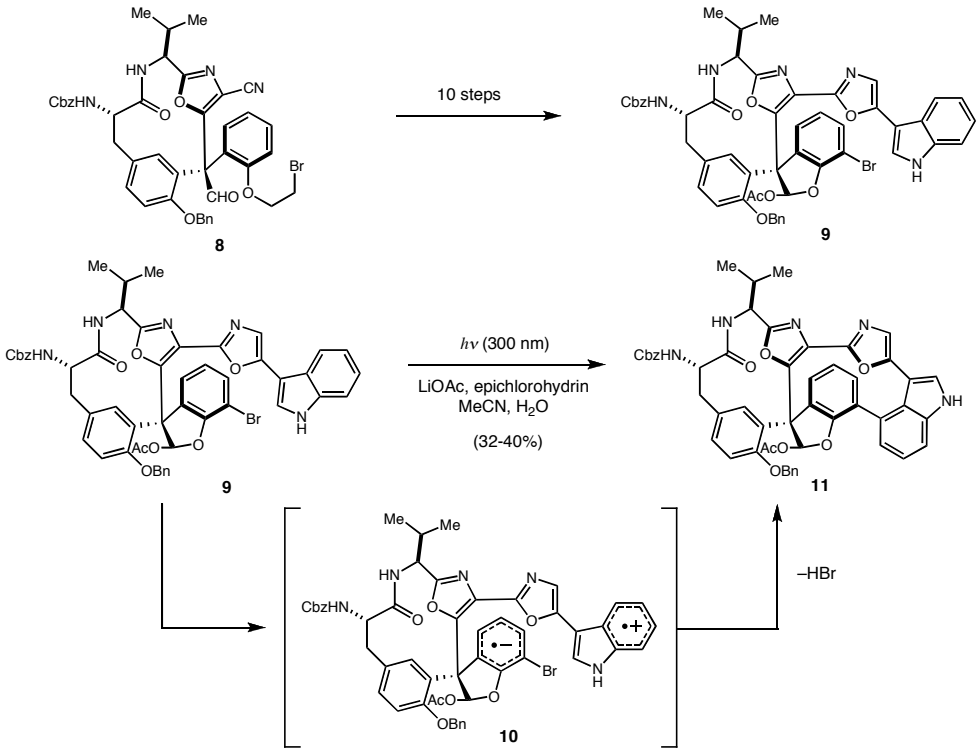


[2] For a report of the synthesis of **1**, see: Li, J.; Jeong, S.; Esser, L.; Harran, P. G. *Angew. Chem. Int. Ed.* **2001**, *40*, 4765–4769.

[3] For a report of the structural revision of **1** to **2**, see: Li, J.; Burgett, A. W. G.; Esser, L.; Amecuza, C.; Harran, P. G. *Angew. Chem. Int. Ed.* **2001**, *4*, 4770–4775.

In the first key transformation, Harran employed a phenol-directed intramolecular Heck reaction to close the left-hand macrocycle, inducing the aryl palladium(II) species derived from **3** to insert the pendant olefin, furnishing thirteen-membered ring **4** after β-hydride elimination (eq 1). Following protection of the phenol, the resulting olefin **5** was diastereoselectively dihydroxylated using a stoichiometric amount of chiral osmium complex **6** (eq 2).[4] Notably, dihydroxylation with an analogous achiral osmium complex predominantly provided the undesired diastereomer. The resulting diol **7** then underwent a stereospecific acid-catalyzed pinacol rearrangement to yield triaryl-substituted aldehyde and the desired ring-contracted twelve-membered macrocycle **8** (eq 3).

Scheme 2: Witkop annulation from Harran's synthesis of nominal diazonamide A



[4] (a) Hanessian, S.; Meffre, P.; Girard, M.; Beuadoin, S.; Sanceau, J.-Y.; Bennani, Y. *J. Org. Chem.* **1993**, *58*, 1991–1993. (b) On the augmented reactivity of similar, formally 20-electron osmium complexes, see: Corey, E. J.; Sarshar, S.; Azimioara, M. D.; Newbold, R. C.; Noe, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 7851–7852.

Aldehyde **8** was then converted to bisoxazole **9** through a conventional 10-step sequence (Scheme 2). Upon irradiation with UV light, it was proposed that bisoxazole **9** would undergo a Witkop-type cyclization to yield to the desired aryl-aryl bond and the intact right-hand macrocycle.[5] This Witkop-type ring closure is an unorthodox and elegant solution to the formation of the D-E biaryl bond. Mechanistically, it is proposed that absorption of a photon by the pendant indole moiety promotes a π electron to a high-energy excited state. This new electronic state has a sufficiently high oxidation potential to transfer an electron to the adjacent aryl bromide, yielding a pair of aryl radical ions (**10)**. Mesolytic cleavage of the carbon-bromine bond in the radical anion then creates a neutral radical, which combines with the pendant indolyl radical cation to form the desired biaryl bond.[6] Accordingly, treatment of bisoxazole with 300 nm light in a buffered solution of aqueous acetonitrile and lithium acetate produced the desired product **11** in a modest 32–40% yield, with most of the remaining mass recovered as unreacted starting material. Remarkably, the B-ring oxazole is created as a single atropisomer with the correct configuration for the natural product. This fact taken together with the relative mildness of the reaction conditions make this a truly innovative and well-conceived solution to an otherwise very difficult bond construction.

Following cyclization, Harran demonstrates that selective, late-stage installation of the aryl chlorides is possible on the intact diazonamide framework of **11**, despite the large number of potentially reactive sites (Scheme 3). This finding was substantial, as it allows all future retrosynthetic analyses to install this functionality to the

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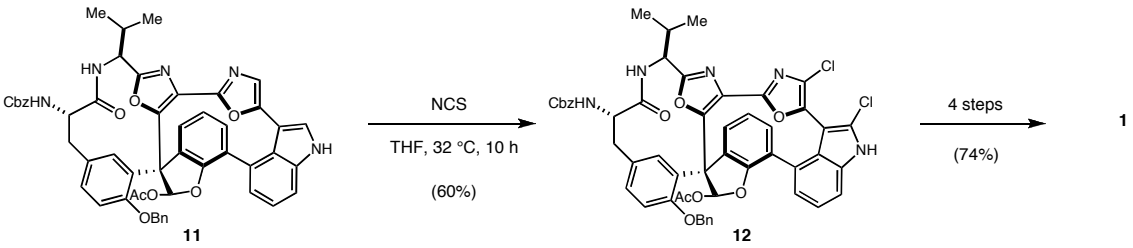
[5] (a)Yonemitsu, O.; Cerutti, P.; Witkop, B. *J. Am. Chem. Soc.* **1966**, *88*, 3941–3945. (b) Masnovi, J. M.; Kochi, J. K.; Hilinski, E. F.; Rentzepis, P. M. *J. Am. Chem. Soc.* **1986**, *108*, 1126–1135.

[6] Maslak, P.; Narvaez, J. N. *Angew. Chem. Int. Ed.* **1989**, *29*, 283–285.

Scheme 3: Chlorination and endgame in Harran's synthesis of nominal diazonamide A



final stages of the synthesis. Lastly, removal of protecting groups and appendage of the valine side chain furnished nominal diazonamide A (**1**), prompting Harran to recognize the necessity of a structural revision.

This synthesis proceeded in 26 steps in the longest linear sequence and in 0.51 % overall yield. Importantly, even though the final target was not truly diazonamide A (**2**), this work established viable strategies toward several of the most daunting features of **2** and many of its key innovations were appropriated and applied to the true natural product in later synthetic campaigns.

III. First-Generation Nicolaou Synthesis

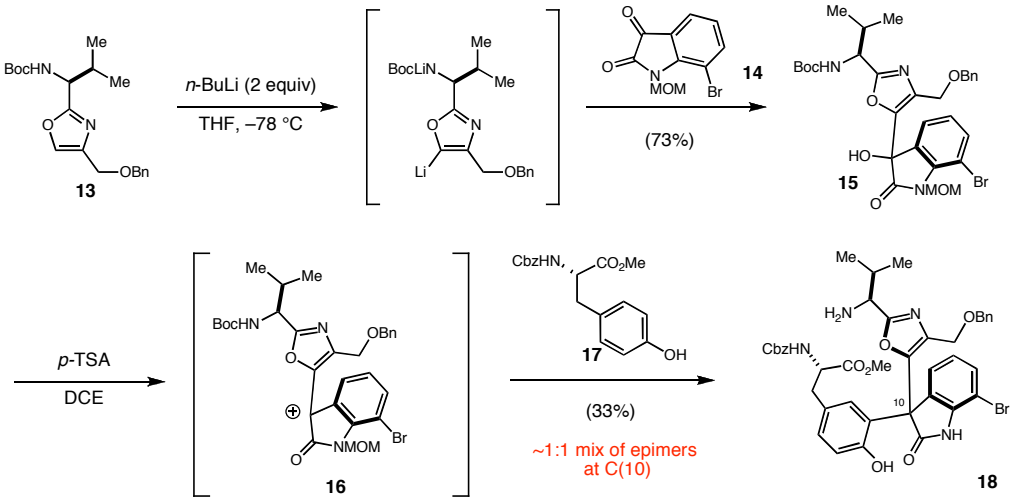
In late 2002, Nicolaou and coworkers at the Scripps Research Institute reported the first total synthesis of the revised structure of diazonamide A.[7,8] In this work, the Nicolaou group chose to construct the C(10) stereocenter via nucleophilic attack of a lithiated oxazole **13** onto the functionalized bromoisatin **14** (Scheme 4). The adduct **15** was then ionized upon subjection to *p*-TSA to form highly stabilized benzylic tertiary carbocation **16** that was subsequently captured by tyrosine derivative **17,** according to the

[7] For the initial communication describing this work, see: Nicolaou, K. C.; Bella, M.; Chen, D. Y.-K.; Huang, X.; Ling, T.; Snyder, S. A. *Angew. Chem. Int. Ed.* **2002**, *41*, 3495–3499.

[8] For a full paper describing this work, see: Nicolaou, K. C.; Chen, D. Y.-K.; Huang, X.; Ling, T.; Bella, M.; Snyder, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 12888–12896.

method described by Olah.[9] Thus, in remarkably short order Nicolaou and coworkers were able to access much of the carbon framework of diazonamide A. However, the product of this reaction sequence (**18)** was formed as a 1:1 mixture of diastereomers at the C(10) quaternary center with relatively poor reaction efficiency (Scheme 4).

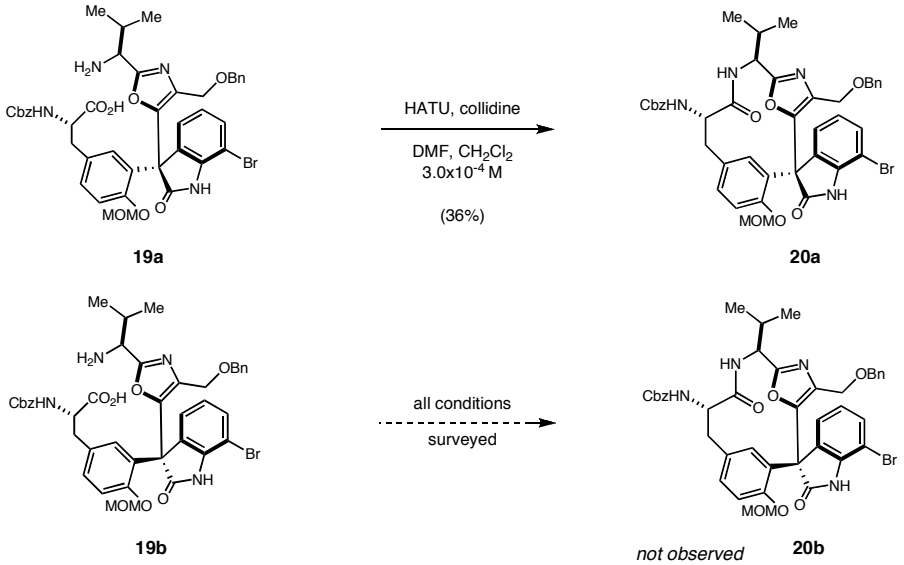
Scheme 4: Original Nicolaou synthesis of C(10) center and heterocyclic core



The two diastereomers of **18** were separated chromatographically and each was carried on independently, as the spectral data offered no insight into which diastereomer possessed the correct C(10) stereochemistry corresponding to that of the natural product. After several straightforward synthetic manipulations, lactamization of **19a** was accomplished under the action of HATU and collidine in a dilute solution of DMF and CH_2Cl_2 to provide the left hand macrocycle, albeit in low yield (eq 4). Notably, only the *S*-configured C(10) diastereomer **19a** underwent reaction while its *R*-antipode **19b** oligomerized or decomposed under all conditions surveyed (eq 5).[10] Fortunately for the

[9] Klumpp, D. A.; Yeung, K. Y.; Prakash, G. K. S.; Olah, G. A. *J. Org. Chem.* **1998**, *63*, 4481–4484.

[10] For a famous example of a macrocyclization dependence on seco acid stereochemistry, see: Woodward, R. B., et al. *J. Am. Chem. Soc* **1981**, *103*, 3213–3215.



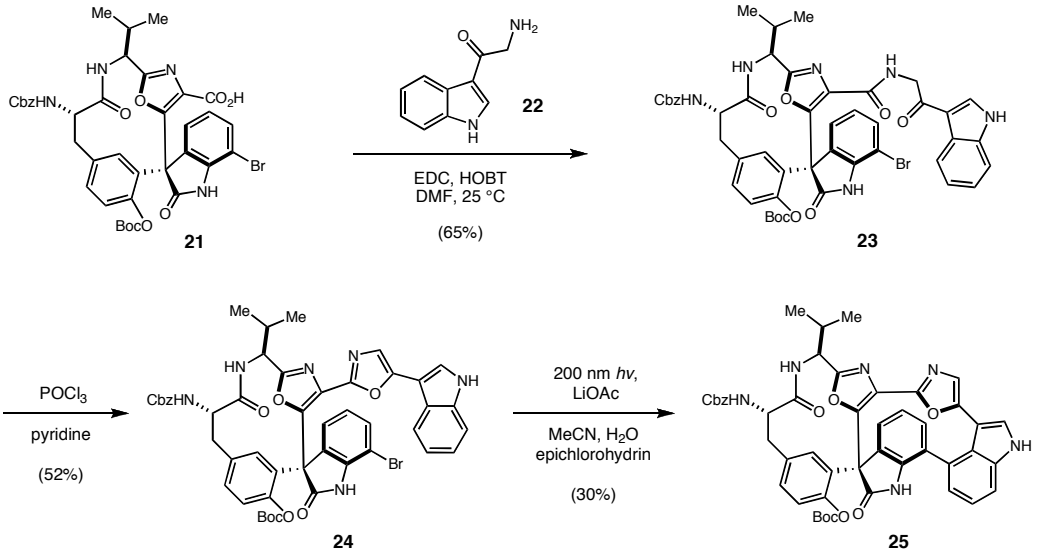
(4)

(5)

Nicolaou group, the *S*-diastereomer was the properly configured C(10) diastereomer and they were able to carry on with the synthesis.

With the left-hand macrocycle in place, efforts turned to closing the right-hand ring. After a series of deprotections and oxidation state changes, carboxylic acid **21** was coupled to the oxidized tryptamine salt **22** (Scheme 5). The ketoamide **23** was then subjected to $POCl_3$ in pyridine to affect a Robinson-Gabriel cyclodehydration, yielding the second oxazole **24** in 52% yield. This sequence installed the complete carbon skeleton of the molecule and provided the precursor for a Witkop-type photocyclization to form the right-hand macrocycle in **25**. This approach to the D-E biaryl synthesis was conceptually appropriated from the Harran synthesis of nominal diazonamide A, but it also differs in certain key aspects. Notably, it demonstrated that this type of reactivity is compatible with the oxindole functionality present in the ring adjacent to the aryl bromide. Also, this cyclization required extremely high-energy 200 nm UV light, as opposed to the 300 nm light source that Harran had used, demonstrating that for these

Scheme 5: Oxazole cyclodehydration and Witkop photocyclization

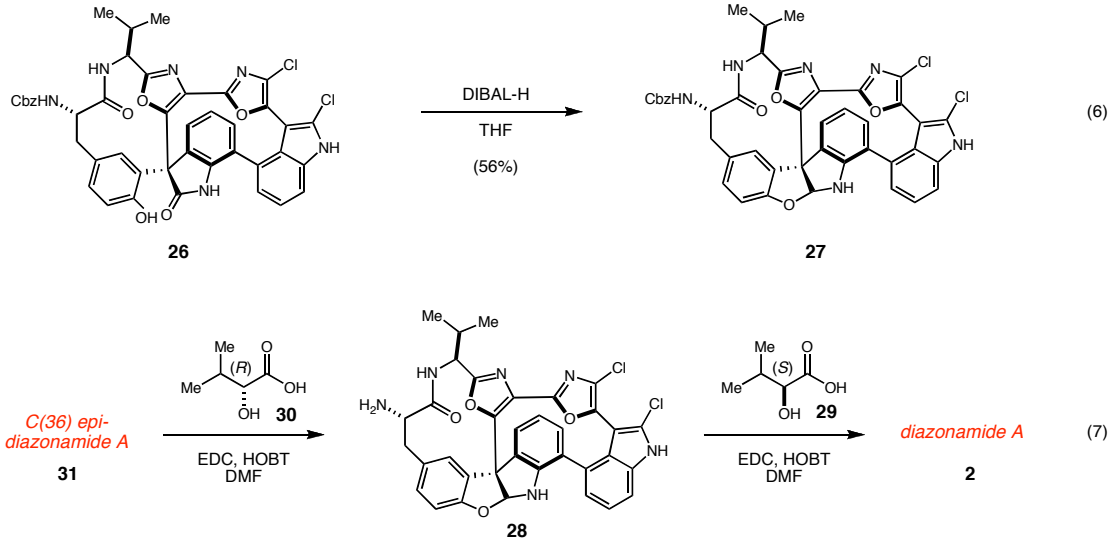


reactions the excitation wavelength has a structural dependence independent from the indole-oxazole chromophore.

Next, the B-ring oxazole and indole C-ring of **25** were selectively chlorinated and the tetracyclic furanoindoline core was closed by reductive cyclization of the H-ring phenol of **26** onto the F-ring oxindole under the action of excess DIBAL to yield **27** (eq 6). After several further deprotection steps, Nicolaou completed the synthesis by coupling **28** to both enantiomers (**29** and **30**) of the hydroxyvaleric acid side chain (eq 7). Diagnostic differences between the two diastereomers in the ^{1}H NMR definitively established the configuration of the C(36) stereocenter in the natural product to be (*S*). Most importantly, the completion of this work demonstrably proved Harran's hypothesis about the true molecular structure of diazonamide A.[3]

In summary, this first completed synthesis consisted of 24 steps in the longest linear sequence, and proceeded in 0.015% overall yield. While this synthesis exhibits a number of interesting transformations, the steps creating the key architectural elements,

such as the C(10) quaternary stereocenter and the twelve-membered rings, are uniformly low yielding. Moreover, from a viewpoint of stereoselectivity, the central C(10) stereocenter was formed as a 1:1 mixture of diastereomers. While this synthesis firmly established the true structure of diazonamide A, it left a great deal of room for improvement with regards to the development of viably scalable and selective synthetic sequences.



IV. Second-Generation Nicolaou Synthesis of Diazonamide A

While efforts toward the synthesis described above were underway, the Nicolaou group was simultaneously working on a second, distinct route toward the target molecule, which they published in mid-2003.[11,12] This second route was strategically distinguished from the first in that the order of macrocycle closure was reversed, instead focusing on

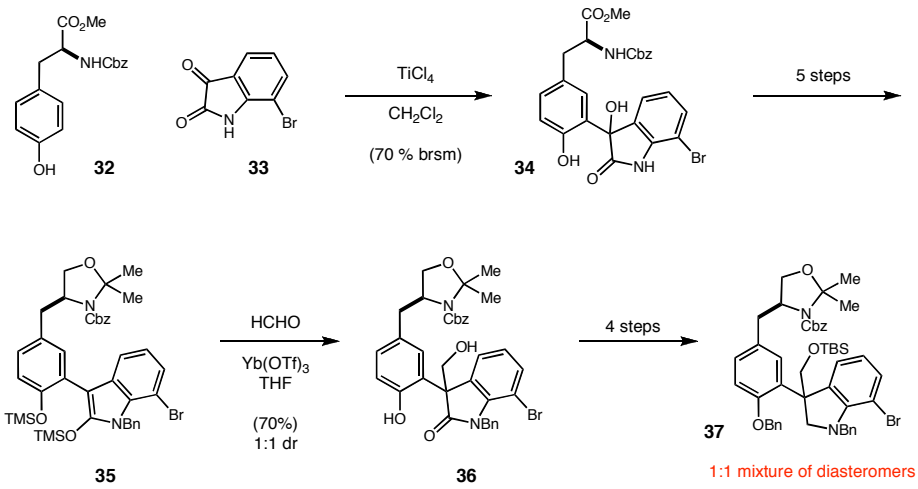
[11] For the initial communication of this work, see: Nicolaou, K. C.; Rao, P. B.; Hao, J.; Reddy, M. V.; Rassias, G.; Huang, X.; Chen, D. Y.-K.; Snyder, S. A. *Angew. Chem. Int. Ed.* **2003**, *42*, 1753–1758.

[12] For a full paper describing this work, see: Nicolaou, K. C.; Hao, J.; Reddy, M. V.; Rao, P. B.; Rassias, G.; Snyder, S. A.; Huang, X.; Chen, D. Y.-K.; Brenzovich, W. E.; Giuseppone, N.; Giannakakou, P.; O'Brate, A. *J. Am. Chem. Soc.* **2004**, *126*, 12897–12906.

initial closure of the right-hand macrocycle. Selected highlights of this work are described below.

This work commenced in a similar fashion to the first–generation Nicolaou synthesis with a Lewis acid-catalyzed addition of tyrosine derivative **32** into 7-bromoisatin **33** to give **34** (Scheme 6). After a series of oxidation state adjustment and protecting group manipulations, siloxyoxindole **35** engages formaldehyde in an aldol coupling to yield **36** and the central C(10) quaternary center, albeit again as an equimolar mixture of diastereomers. The oxindole functionality is then reduced to its corresponding indoline form and the phenol protected to yield **37**.

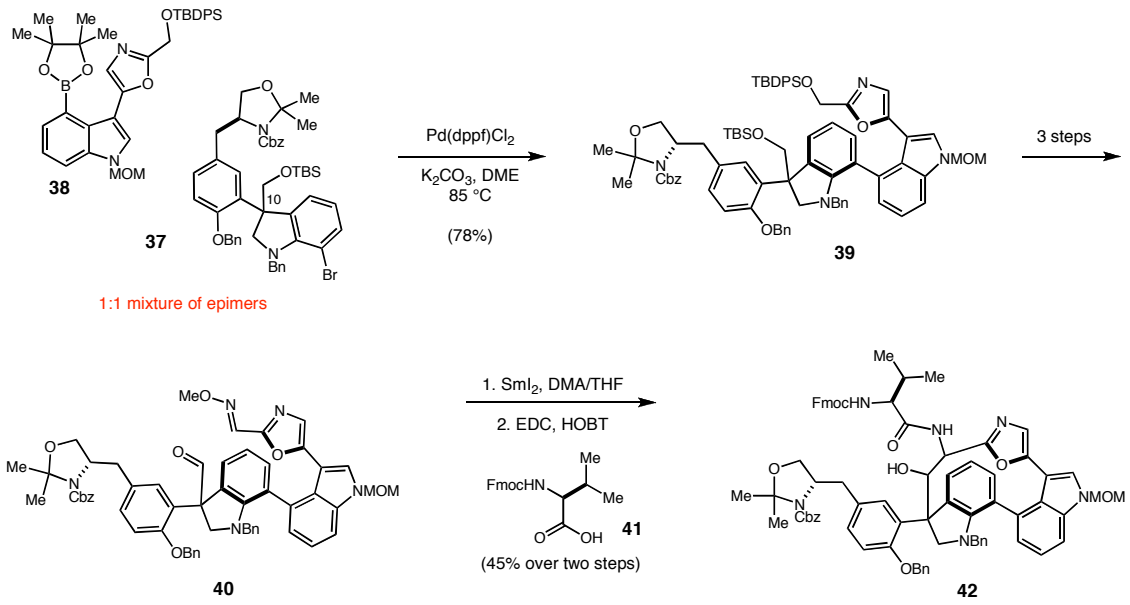
Scheme 6: Formation of C(10) center in second-generation Nicolaou synthesis



Indoline **37** is next coupled to boronic ester **38** in a palladium-catalyzed Suzuki coupling, establishing the C(16)–C(18) biaryl bond of **39** (Scheme 7). The silyl ethers were then removed and the resulting alcohols were oxidized to their corresponding aldehydes. Treatment of the resulting dialdehyde with *O*-methyl hydroxylamine selectively generated the key oxime aldehyde intermediate **40**. Treatment with SmI_2 led to a hetero-pinacol coupling to form the right-hand macrocycle with concomitant

cleavage of the N-O bond. Coupling of the newly formed amine with a *N*-protected valine **41** using standard peptide coupling procedures gave hydroxy amide **42** in a combined yield of 45% over the two steps.

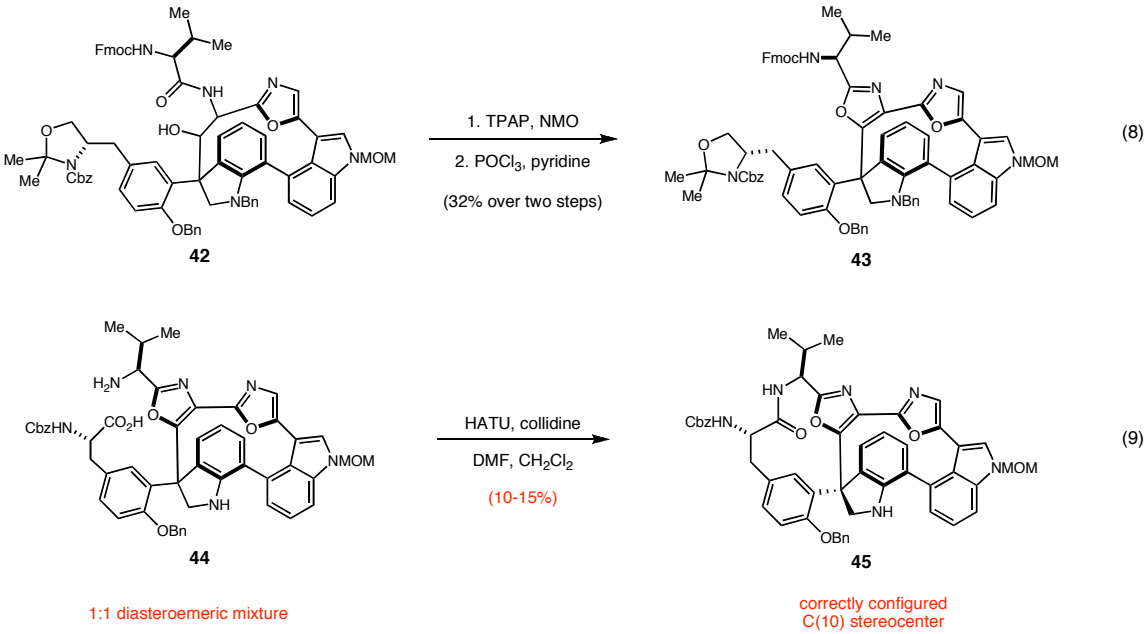
Scheme 7: Suzuki coupling and hetero-pinacol ring closing



Oxidation of the free hydroxyl group was followed by treatment with $POCl_3$ in pyridine to give the A-ring oxazole of **43** in 32% yield over the two steps based on recovered starting material (eq 8). However, during this sequence the C(10) diastereomers were not chromatographically resolvable, and as such all of these intermediates were carried through the subsequent synthetic transformations as a mixture of diastereomers.

Deprotection of the mixed acetal in **43**, oxidation to the free carboxylic acid and liberation of the valine-derived primary amine set the stage for the second macrocyclization of **44**. Unfortunately, this step proved much more difficult than it had in the previous synthesis. This was attributed by the authors to constraints resulting from the right-hand ring already being in place. In the end, treatment of **44** with HATU and

collidine in dilute DMF/CH_2Cl_2 produced the desired macrocycle **45** in only 10–15% yield (eq 9). Once again this step served to resolve the C(10) epimers, as only the correctly configured diastereomer of **44** underwent ring closure.

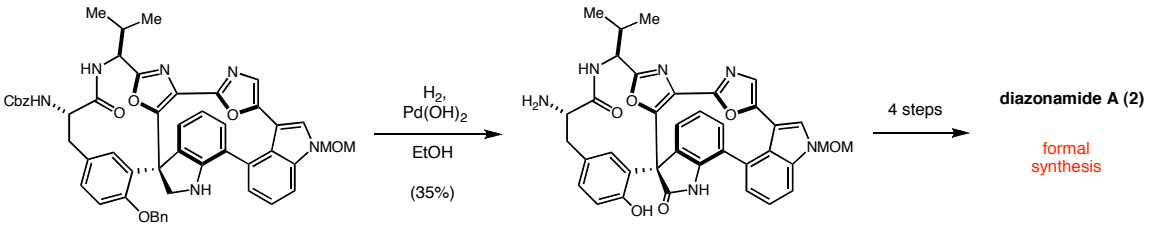


(8)

(9)

At this juncture it became necessary to reinstall the oxindole moiety of the F-ring. Notably, this functionality had been present in prior intermediates in the synthesis, yet had been reductively excised to facilitate the success of other downstream transformations. The Nicolaou group was fortunate to find that the indoline **45** was unexpectedly oxidized to its corresponding oxindole under the nominally reducing hydrogenative conditions employed to remove the benzyl ether of **45**, producing oxindole **46** in 35% yield (Scheme 8). After a three-step sequence this oxindole was transformed into an intermediate from the first-generation synthesis, completing a late-stage formal synthesis of diazonamide A. Taking synthetic **43** on to the natural product **2** furnishes a 32-step synthesis in the longest linear sequence proceeding in 0.017% overall yield.

Scheme 8: Second-generation endgame and completion of late-stage formal synthesis



42 **43**

In a critical sense, this synthesis was substantially longer than its predecessor, but proceeds with similarly low overall efficiency. With regard to addressing the key synthetic hurdles, the late stage amide coupling to close the left-hand macrocycle proceeds in only 10% yield, representing a severe hurdle to making meaningful quantities of diazonamide A in this manner. The fact that this lactamization step also serves to resolve the C(10) diastereomers shines an even harsher light on the strategic decision to synthesize this central structural feature as a 1:1 mixture. However, the reductive pinacol closure to form the right-hand macrocycle proved to be an interesting and more efficient strategic disconnect relative to the Witkop-type chemistry described previously. Yet it was still unlikely that either of these first two completed syntheses would be able to reasonably provide the material needed to establish the biological underpinnings of diazonamide A's activity.

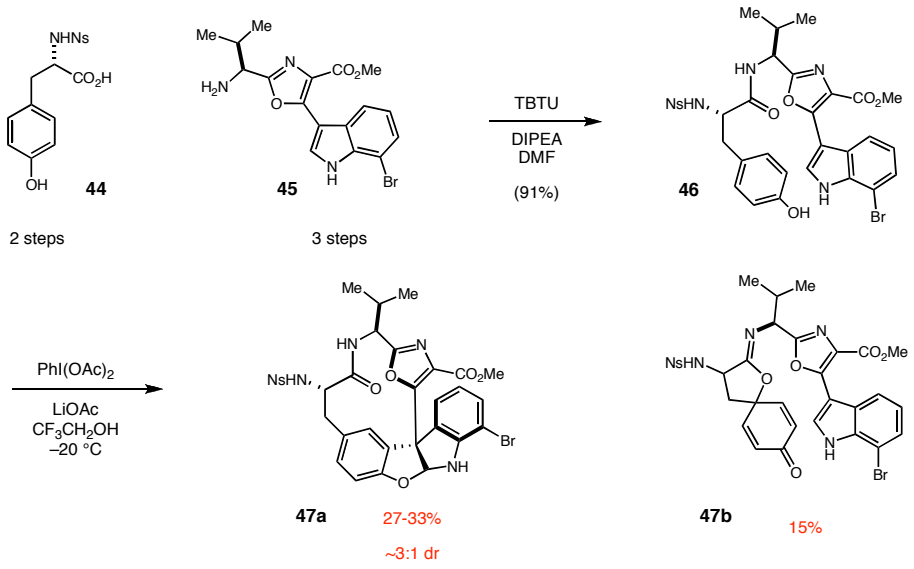
V. Harran's Synthesis of Diazonamide A

Having contributed so much to the early synthetic work in the diazonamide field and proposing the true structure of the natural product, it was only fitting that Harran and coworkers reported a third synthesis of the revised structure in late 2003.[13] In a process

[13] Burgett, A. W. G.; Li, Q.; Wei, Q.; Harran, P. G. *Angew. Chem. Int. Ed.* **2003**, *42*, 4961–4966.

that may mimic the biosynthesis of the tetracyclic E-F-G-H core, the key disconnection in this synthesis is an intramolecular oxidative annulation of tyrosine across the enamine-like π bond of a pendant indole to create the intact tetracyclic core, the central quaternary stereocenter, and the left-hand macrolactam of diazonamide A simultaneously. This idea was reduced to practice in the fifth linear step of the synthesis by subjecting phenol **46** to bis(acetoxy)iodosobenzene in cold trifluoroethanol to yield **47** as a 3:1 mixture of diastereomers in roughly 30% yield along with 15% of undesired product **48** (Scheme 9).

Scheme 9: Haran's synthesis of the E-F-G-H rings and the C(10) center

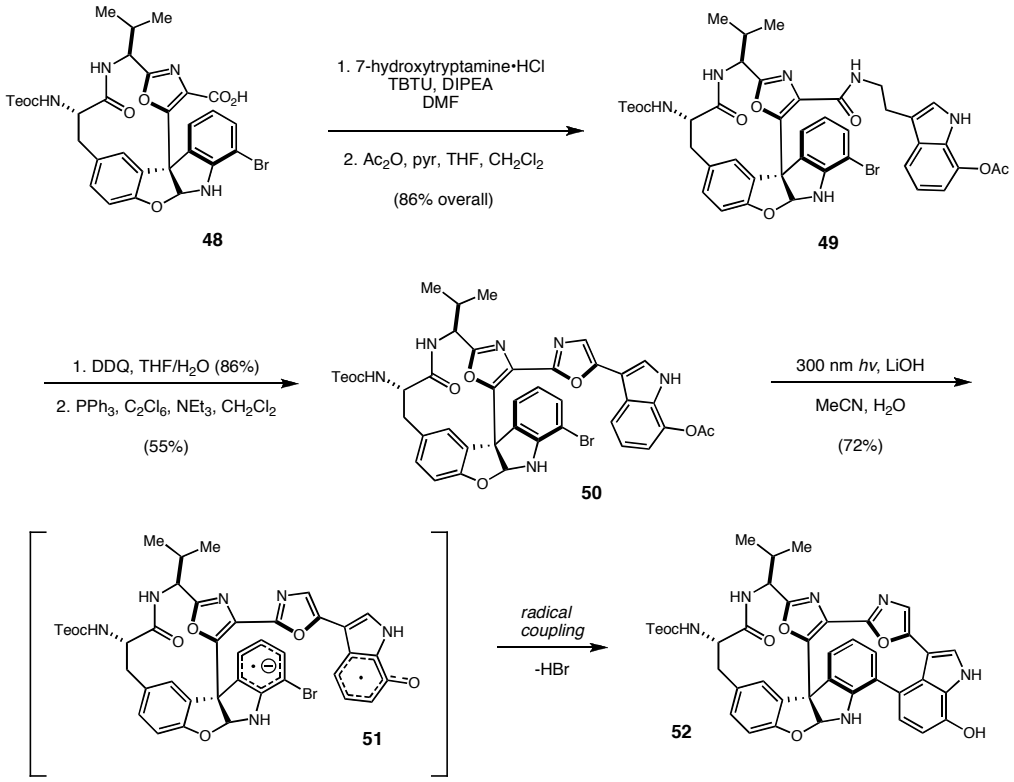


Mechanistically this process is believed to occur by coordination of the phenolic oxygen to the hypervalent iodine species, rendering the *ortho*-position of the aromatic ring electrophilic. The 3-position of the pendant indole then adds to this nascent electrophilic site. Following tautomerization, the phenol then closes down into the resulting indolium ion, yielding the desired product **47a**. Despite the low yield and the modest diastereoselectivity, this step is able to address three of the most vexing features

of the diazonamides in a single well-conceived stroke, and represented by far the most rapid, diastereoselective, and efficient entry into the diazonamide A core to date.

After a number of straightforward synthetic manipulations, **47** was elaborated to the free carboxylic acid **48**, which was successfully coupled to the HCl salt of 7-hydroxy tryptamine (Scheme 10). Subsequent acetylation of the free phenol was followed by benzylic oxidation of the 3' position of the indole **49** by DDQ in aqueous THF.[14] The resulting ketoamide was then cyclized to the desired oxazole **50** using the conditions reported by Wipf.[15] This set the stage for a slightly modified and improved Witkop cyclization from the one encountered in the first-generation Nicolaou synthesis. Basic

Scheme 10: Haran's Witkop closure of the right-hand macrocycle



[14] Oikawa, Y.; Yonemitsu, O. *J. Org. Chem.* **1977**, *42*, 1213–1216.

[15] Wipf, P.; Yokokawa, F. *Tetrahedron Lett.* **1998**, *39*, 2223–2226.

hydrolysis of the acetoxy group of **50** *in situ* followed by photo-irradiation of the resulting phenolate produced the right-hand macrocycle **52** in a yield of 72%. The greater electron density of the indole unit resulting from the anionic phenolate substituent results in a higher propensity for the indole to transfer an electron to the bromoindoline, as in **51**, providing much higher yields than were realized in either Harran's previous synthesis toward the proposed structure or the first Nicolaou synthesis. This augmented efficiency was considered to be ample justification for the inclusion of the otherwise extraneous phenol moiety on the indole.

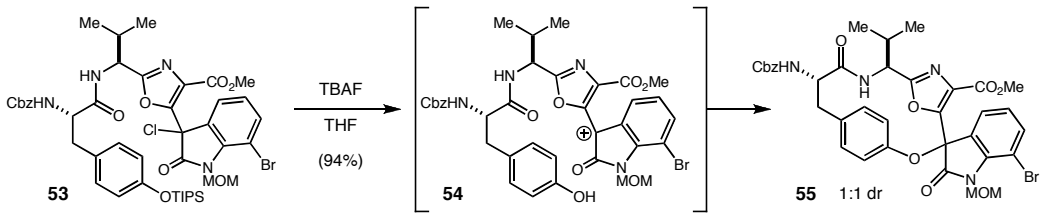
The phenolic oxygen was then excised via hydrogenolysis of its corresponding triflate. This was followed by the bischlorination and removal of the C(2) amine protecting group. Peptide coupling of the side chain **29** completed the shortest synthesis to date in a total of 21 steps in the longest linear sequence (19 distinct isolation steps) and an overall yield of 0.91%. This synthesis sets a high bar for all forthcoming syntheses to reach. Harran's synthesis is a result of years of work toward these molecules, but the final result is a remarkable synthetic accomplishment; elegant, well executed, and concise.

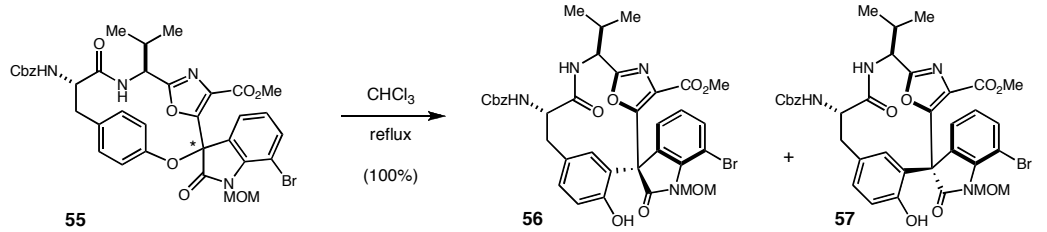
VI. Magnus' Formal Synthesis of Diazonamide A

In late 2007, Magnus and coworkers at the University of Texas at Austin reported a formal total synthesis of diazonamide A that intercepted an advanced intermediate in the first-generation Nicolaou synthesis.[16] The highlights of this work begin with **53**, which upon treatment with TBAF yields ether **55** via intermediate **54** (Scheme 11). **55** then undergoes an unusual O–C migration that converts benzhydryl ether to the desired

[16] Cheung, C.-M.; Goldberg, F. W.; Magnus, P.; Russell, C. J.; Turnbull, R.; Lynch, V. *J. Am. Chem. Soc.* **2007**, *129*, 12320–12327.

Scheme 11: Magnus' synthesis of the left-hand macrocycle and the C(10) center





	desired	***undesired***
(*R*) - C(10) diastereomer	84	16
(*S*) - C(10) diastereomer	56	44
1:1 mix of C(10) diastereomers	70	30

quaternary center in **56** and **57**. The stereoselectivity of this rearrangement step was dependent on the stereochemical configuration of the starting ether **55**, the nature of solvent and the reaction temperature. The best results with regard to stereoselectivity and conversion were found to occur in refluxing chloroform, giving 100% yield of the desired product as 7:3 mixture of diastereomers (**56**/**57**) in favor of the desired isomer.

Magnus then demonstrated that **56** could be converted in three steps to an intermediate in the first Nicolaou synthesis that then requires 13 further steps to furnish the natural product **2**. As such, if carried to completion this route would be 23 steps in its longest linear sequence. This work is remarkable in that it provides exceptionally efficient access to the left-hand macrocycle through a highly innovative and original transformation, but with poor diastereoselectivity. Interestingly, Nicolaou had reported attempting a similar type of cyclization with a nearly identical substrate, albeit under different conditions, without any success in his first-generation synthesis.

V. Conclusion

These summaries provide the context against which the MacMillan studies towards diazonamide A were both conceived and executed. The work described above acts not only to describe the reactivity of this molecule, but also to point out the considerable difficulties inherent in its synthesis. This in turn gives direction and purpose to our own work, to solve these standing problems and to arrive at general solutions that will be of interest and use to the synthetic community at large. Our efforts toward these ends are described in the remaining chapters of this thesis.

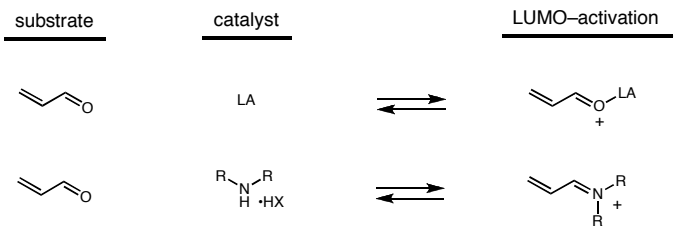
Chapter 3

First-Generation MacMillan Synthesis of Diazonamide A: Strategy Development and Initial Synthetic Investigations

I. Background

In 2001, the MacMillan group described the development of a novel, powerful and general platform of asymmetric catalysis based on the reactions of transient α,β-unsaturated iminium ions, formed from the rapid and reversible condensation of secondary amines with enals. This mode of activation was remarkable in that the reaction catalysts themselves were simple organic molecules.[1] This bucked the conventional wisdom that asymmetric catalysis was exclusively the domain of transition metal complexes and enzymes, and explicitly conceptualized the both the notion and the value of organocatalysis as an undeveloped area of study. Indeed, the disclosure of iminium catalysis, along with the work of Barbas and List in the rejuvenation of proline catalysis, is widely credited with being a foundational contribution in establishing this active and expanding field.[2]

Figure 1: LUMO-lowering in Lewis acid catalysis and iminium catalysis

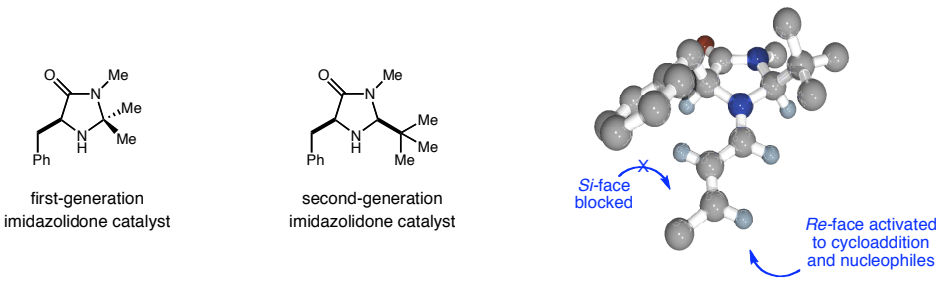


[1] Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243–4244.

[2] List, B.; Lerner, R.; Barbas III, C. F. *J. Am. Chem. Soc*. **2000**, *122*, 2395–2396.

Conceptually, the viability of asymmetric iminium catalysis was founded on two central assumptions. First, iminium formation should emulate the LUMO-lowering electronic activation and equilibrium dynamics attendant to traditional Lewis acid catalysis, providing a means for differential substrate activation (Figure 1). Secondly, if appropriately chosen, the chiral amine should enable high levels of asymmetric induction in bond-forming events by creating a well-defined chiral environment around the reaction center. Specifically, an effectively designed amine would have both to control the geometry of the iminium with respect to the catalyst framework and to direct the approach of nucleophiles to a single enantioface of the aldehyde electrophile. Implementation of these design criteria led to the development of a family of chiral imidazolidinone catalysts, which have been demonstrated to be efficient and highly enantioselective catalysts for a wide range of conjugate addition and cycloaddition processes (Figure 2).[3]

Figure 2: Chiral imidazolidinone catalysts in iminium chemistry



In fact more than forty distinct transformations that give enantiomeric excesses in upwards of 90% have been developed using imidazolidinone-based iminium catalysis.[4]

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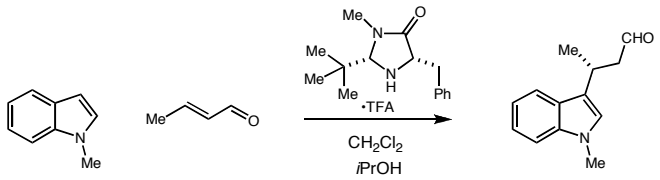
[3] For a complete recounting of the historical development of the imidazolidinone-based catalysts, see; Austin, J. F. *Ph.D. Thesis*, California Institute of Technology, 2005.

[4] For a recent review of asymmetric iminium chemistry, see: Lelais, G.; MacMillan, D. W. C. *Aldrich Chimica Acta* **2006**, *39*, 79–87.

Importantly, many of these reactions have no traditional analogy in Lewis acid catalysis, a testament to the power of iminium activation as not only a practical tool for the synthesis of chiral molecules, but also as a platform for the discovery of novel synthetic transformations. One particularly successful and important advance in this regard was the discovery that iminium catalysis was amenable to the asymmetric Friedel-Crafts addition of electron-rich indoles into α,β-unsaturated aldehydes.[5] The benzylic indole stereocenter is prevalent in both natural products and medicinal agents, and this technology has been recognized as a seminal advance in the catalytic, asymmetric construction of this particular motif.[6] A representative example of this reaction is shown below in equation 1.



(1)

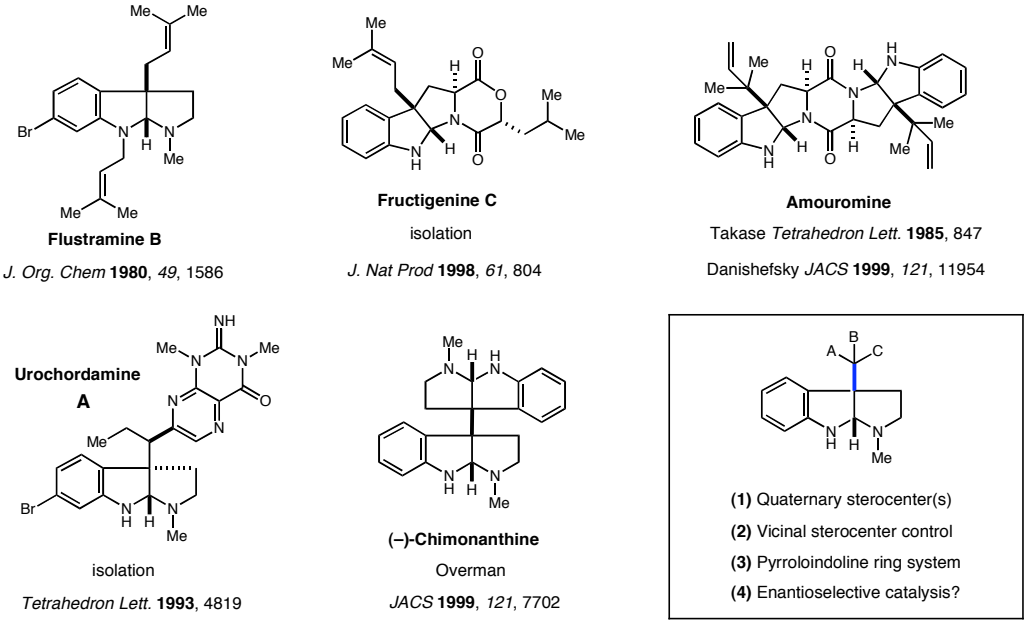
Having established the viability and generality of this method, the MacMillan group sought to find compelling applications for its use in the construction of structurally complex targets. One particularly attractive class of indole-based alkaloids that seemed well suited to this end is the pyrroloindoline family (Figure 3). Derived from oxidative transformations of the amino acid tryptophan and its derivates, the tricyclic pyrroloindoline core is a widely represented structural motif. These molecules have received a great deal of attention over the past two decades due to their interesting biological properties and unusual structures, and significant advances have been made toward their synthesis. Yet, despite all this prior work, no direct, catalytic asymmetric

[5] Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172–1173.

[6] King, H. D.; Meng, Z.; Denhart, D.; Mattson, R.; Kimura, R.; Wu, D.; Gao, Q.; Macor, J. E. *Org. Lett.* **2005**, *7*, 3437–3440.

approaches to the pyrroloindoline core from simple tryptamine precursors had been reported. Accordingly, the MacMillan group felt that a generic solution to this conspicuous gap had the potential to conceptually trivialize future retrosynthetic analysis of these targets.

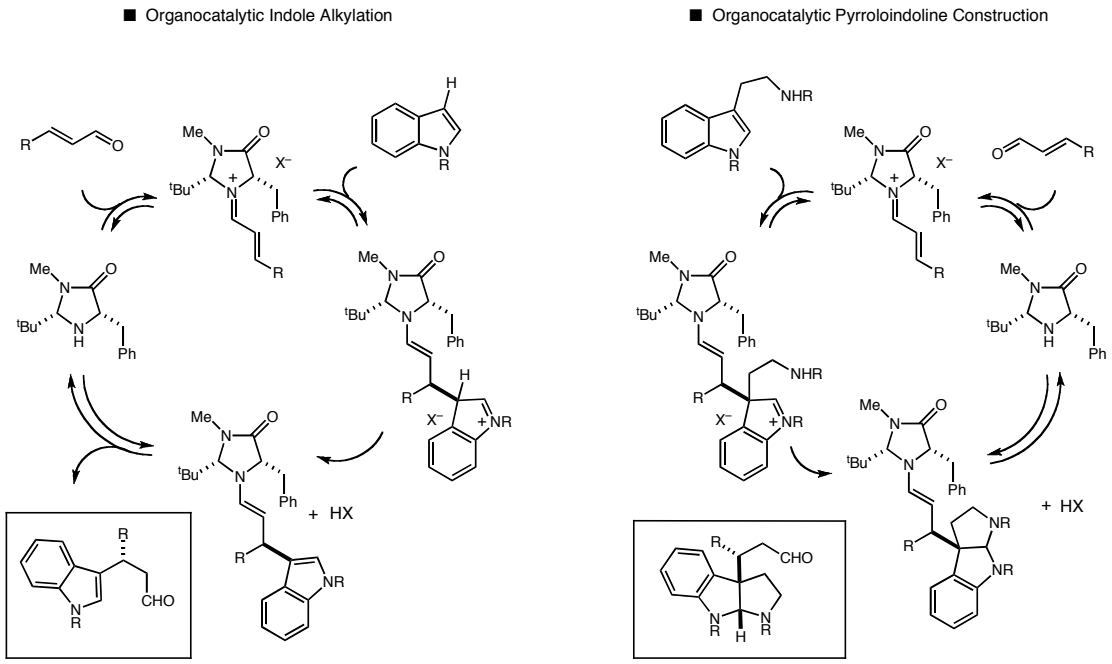
Figure 3: Representative pyrroloindoline natural products



The mechanistic outline for the proposed organocatalytic pyrroloindoline synthesis is outlined in contrast to the conventional catalytic cycle for iminium-catalyzed Friedel-Crafts additions in Figure 4. While highly analogous, these manifolds are differentiated by the fact that in the indole additions, the nucleophilic 3-position of the heterocycle which undergoes alkylation bears a proton substituent. Following carbon-carbon bond formation, this proton is abstracted by the conjugate base of the acid cocatalyst, regenerating aromaticity and rendering the alkylation irreversible. However, in the pyrroloindoline case, alkylation renders the C(3) position of the tryptamine quaternary, precluding the deprotonation pathway. Rather, following alkylation, the

amine nucleophile on the end of the two-carbon tether cyclizes onto the pendant indolium ion, generating the tricyclic product.

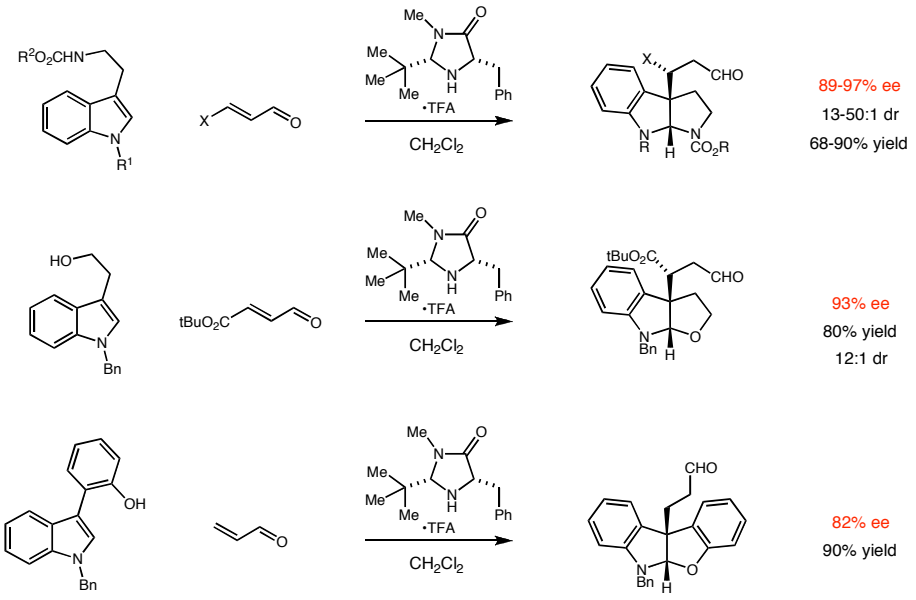
Figure 4: Organocatalyzed pyrroloindoline construction: catalytic cycle



When this mechanistic scheme was reduced to practice, this reaction was found to be general, efficient, and highly enantioselective.[7] A wide variety of sterically and electronically diverse enals and tryptamines participated, allowing for the asymmetric construction of a wide variety of pyrroloindoline structures in a single step from trivial starting materials using an inexpensive amine catalyst (Figure 5). Yet in the context of the diazonamides, perhaps the most pertinent discovery to arise from this chemistry was the finding that pendant amines are not the only competent terminal nucleophilic traps. Specifically, alcohols and phenols were found to cyclize with similarly high levels of efficiency and selectivity to form tri- and tetracyclic furanoindoline products (Figure 5).

[7] Austin, J. F.; Kim, S. G.; Sinz, C. J.; Xiao, W. J.; MacMillan, D. W. C. *Proc. Nat. Acad. Sci.* **2004**, *101*, 5482–5487.

Figure 5: Organocatalytic pyrroloindoline and furanoindoline formation



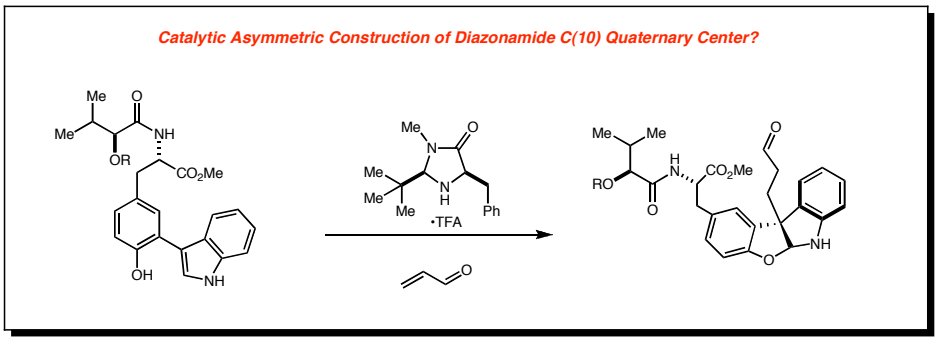
Remarkably, the MacMillan lab's development of asymmetric access to these interesting, but admittedly obscure, furanoindoline heterocycles was concurrent with Harran's disclosure of his synthesis of nominal diazonamide A and its associated structural revision described in Chapters 1 and 2.[8] Seemingly overnight, the MacMillan group found itself in possession of an almost tailor-made and highly original retrosynthetic insight into the asymmetric catalytic construction of the tetracyclic core of these daunting targets. In particular, this chemistry provided a unique opportunity to enable a truly stereoselective synthesis of the C(10) quaternary center, the central structural feature of the diazonamides, and the one which had yet to find a suitably selective synthetic solution.

As these opportunities were uniquely enabled by the development of iminium catalysis, we felt they exemplified our firm belief that this new technology was

[8] Li, J.; Burgett, A. W. G.; Esser, L.; Amezcua, C.; Harran, P. G. *Angew. Chem. Int. Ed.* **2001**, *40*, 4770–4774.

generative, and could impact difficult synthetic problems by enabling chemists to design and achieve otherwise unprecedented bond constructions. Moreover, we felt such a compelling application of our iminium technology would highlight the virtues of its chemoselective activation mode and attendant functional orthogonality, testifying to its considerable potential for use in late-stage, complex, or highly functionalized settings. These ideas guided our thinking, provided our inspiration, and became the conceptual cornerstone of our strategy. The remainder of this thesis will detail our considerable progress towards these ends.

Figure 6: Organocatalytic retrosynthesis of diazonamide A core

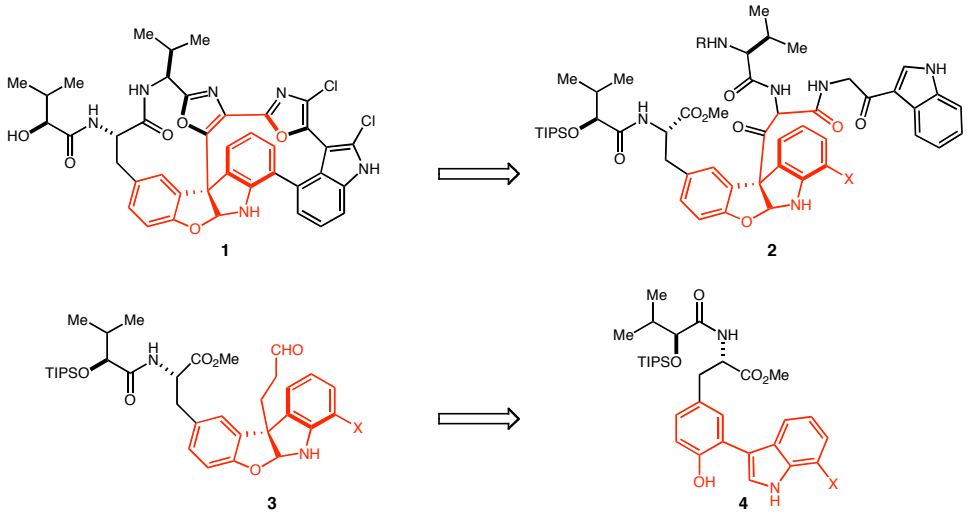


II. Retrosynthetic analysis

With the centerpiece of our strategy outlined above, we needed to devise a way to advance the product of our organocatalytic process on to the natural product (Figure 6). Working retrosynthetically from **1**, we planned to install the aryl chlorides at a late stage based on the precedent from Harran's synthesis of nominal diazonamide A (Figure 7).[9] Next we decided to adopt a strategy of building the entire carbon skeleton of the target prior to closure of either of the two twelve-membered macrocycles. We felt such a

[9] Li, J.; Jeong, S.; Esser, L.; Harran, P. G. *Angew. Chem. Int. Ed.* **2001**, *40*, 4765–4769.

Figure 7: Retrosynthetic outline of MacMillan approach to diazonamide A

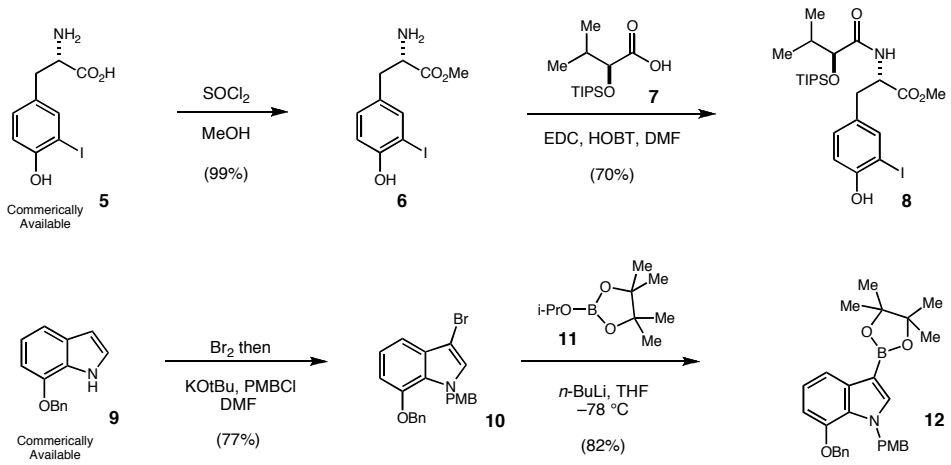


strategy would afford the greatest possible flexibility in addressing issues of endgame sequencing. While we recognized that such an approach risks delaying two of the most difficult bond formations until a late stage in the synthesis, we felt the risk was well justified by the open-ended and adaptable endgame strategy. From such an intermediate, we felt that hydrolysis of the tryptamine amide and the central oxazole would furnish an amino ketone **2** that should be easily derived from oxidative manipulations of the product of our organocatalytic alkylation **3**. We envisioned that **3** could arise from biaryl **4**, which in turn could be accessed readily by the palladium-catalyzed coupling of suitably functionalized tyrosine and indole derivatives.

III. First-Generation Synthesis

The synthesis commences with the quantitative esterification of **5** to give methyl ester **6** (Scheme 1). Though compound **6** is commercially available, this one-step protocol proved more economical to generate the large quantities of material necessary to develop the synthesis. Amino ester **6** was coupled to (*S*)-2-triisopropylsiloxy-3-methylbutanoic

Scheme 1: Synthesis of Suzuki precursors



acid **7** using standard peptide coupling conditions to yield aryl iodide **8** in two steps and an overall yield of 70%.[10]

The synthesis of the indole coupling fragment was then undertaken by selectively brominating the C(3) position of commercially available 7-benzyloxyindole **9** using Br_2 in DMF according to the procedure of Palla.[11] This was followed by PMB protection of the indole nitrogen using PMBCl under the action of potassium *tert*-butoxide in DMF. The similarity of the reaction conditions for these two steps allowed them to be carried out sequentially in a single reaction flask to give yield of the desired product **10**, which was subsequently recrystallized to purity in 77% yield. This protection step was followed by lithium-halogen exchange on the indole bromide under the action of *n*-butyllithium in THF at –78 °C. The resulting aryl lithium was quenched with pinacol-derived borolane **11** to provide boronic ester **12** in 82% yield following recrystallization. This scalable procedure furnishes the second partner for the Suzuki cross coupling reaction in two steps without the need for any chromatographic purification.

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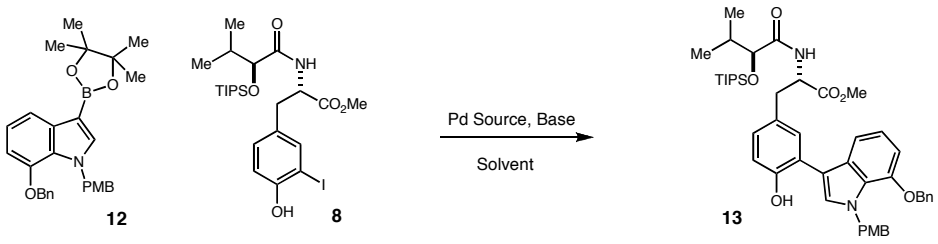
[10] The one-step synthesis of **7** is described in the supporting information.

[11] Bocchi, V.; Palla, G. *Synthesis-Stuttgart* **1982**, 1096–1097.

With these coupling partners in hand, attention turned to their palladium-catalyzed union. The proposed Suzuki coupling step is somewhat unorthodox given the phenolic oxygen adjacent to the iodide on the tyrosine component **8**. Under the basic reaction conditions required for successful Suzuki coupling it was postulated that the nascent phenoxide would greatly retard the rate of oxidative addition by increasing the electron density in the π system of the aromatic ring. However, careful optimization of the reaction conditions showed that employing 7.5 mol% $Pd(dppf)Cl_2$ in aqueous dioxane at 45 °C using K_3PO_4 as a base delivered 82% of the desired product **13** (Table 1, entry 9).

Table 1: Optimization of Suzuki coupling

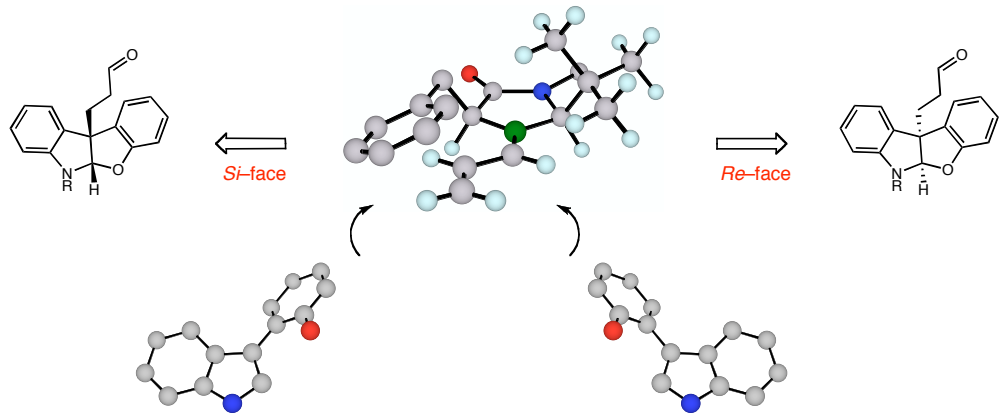


Entry	Pd Source	Base	Temp	Solvent	Conc	Yield
1	$Pd_2(dba)_3$ + $Pd(PtBu_3)_2$	KF	40 °C	THF	0.2M	0%
2	$Pd_2(dba)_3$ + $Pd(PtBu_3)_2$	KF	40 °C	Dioxane	0.2M	0%
3	$Pd(PPh_3)_2Cl_2$	K_3PO_4	40 °C	DME/H_2O	0.1M	33%
4	$Pd(OAc)_2$ + dppf	K_3PO_4	40 °C	DME/H_2O	0.1M	33%
5	$Pd(dppf)Cl_2$	KOAc	40 °C	DME/H_2O	0.1M	10%
6	$Pd(dppf)Cl_2$	K_2CO_3	40 °C	DME/H_2O	0.1M	20%
7	$Pd(dppf)Cl_2$	K_3PO_4	40 °C	DME/H_2O	0.1M	60%
8	$Pd(dppf)Cl_2$	K_3PO_4	40 °C	Dioxane/H_2O	0.2M	78%
9	$Pd(dppf)Cl_2$	K_3PO_4	45 °C	Dioxane/H_2O	0.2M	82%

The success of this cross coupling step provided us with ample material to explore the key organocatalytic construction of the C(10) quaternary carbon stereocenter. Several

features of this key asymmetric transformation are highly unusual and, as such, are worthy of further description. Namely, since acrolein has no nonhydrogen β-substituent, the factors controlling stereoinduction for this electrophile are, by necessity, distinct from those controlling additions to all other enals. Specifically, although the acrolein-based iminium ion is a chiral electrophile, none of its carbons become stereogenic upon alkylation. Rather, in the pyrroloindoline case, the C(3) position of the indole nucleophile becomes quaternary. As such, to induce asymmetry the catalyst must effectively dictate which π-face of the indole nucleophile engages the electrophile in the C-C bond-forming event (Figure 8).

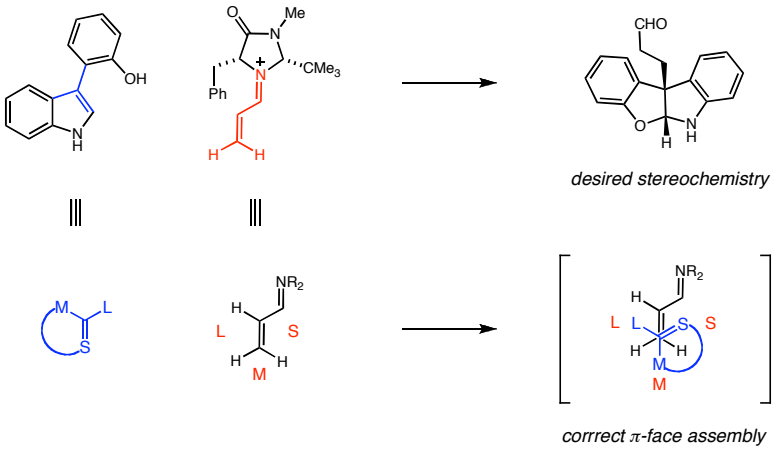
Figure 8: Asymmetric induction in organocatalytic furanoindoline formation



This is a completely unprecedented mode of asymmetric induction that our laboratories have yet to fully investigate. Indeed, studying and understanding the undoubtedly subtle factors that enforce enantiocontrol in these reactions would likely necessitate intense computational investigations. However, in instances where acrolein is used as an electrophile, a heuristic has been devised that correctly predicts the sense of

asymmetric induction.[12] This model requires a tripartite division of both the iminium ion electrophile and the biaryl nucleophile into sectors of increasing steric demand about the two carbon atoms undergoing bonding in the transition state (Figure 9). Aligning the small, medium, and large sectors on each reactant predicts which face of the π-nucleophile adds to the iminium ion. Importantly, this model is not assumed to be an accurate representation of the actual transition state, yet it correctly corroborates all of Austin's original results. As such, we determined that the (*R,R*)-series of the catalyst would be required to give the correct absolute stereochemistry for the diazonamide C(10) center.

Figure 9: Heuristic for assessing enantiocontrol in additions to acrolein

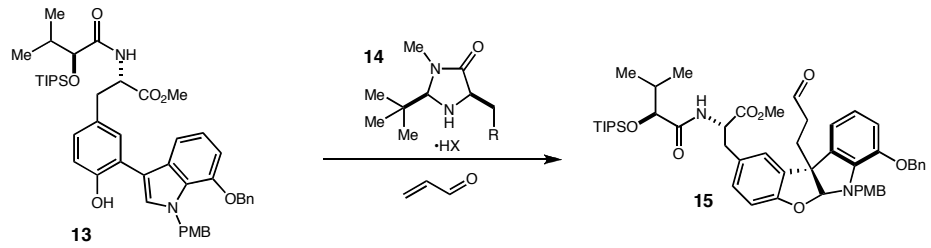


Model systems pointed to the use of the trifluoroacetic acid salt of catalyst **14** in CH_2Cl_2 and MeOH with excess acrolein as being optimal for maximum stereoselection in the alkylation step. However, for **13**, while these conditions did prove highly efficient, the observed diastereoselectivities were relatively poor, typically being 3:1 (Table 2, entry 1). While this provided ample material to explore downstream chemistry, it was felt that, since catalyst-controlled C(10) construction was a major goal of this work, more

[12] Austin, J. F. *Ph.D. Thesis*, California Institute of Technology, 2005, 48–49.

optimization would have to be done to rectify these poor stereoselectivities. With this in mind, a variety of catalyst architectures, solvents, and co-catalysts were evaluated. Selected results of these studies are summarized in Table 2.

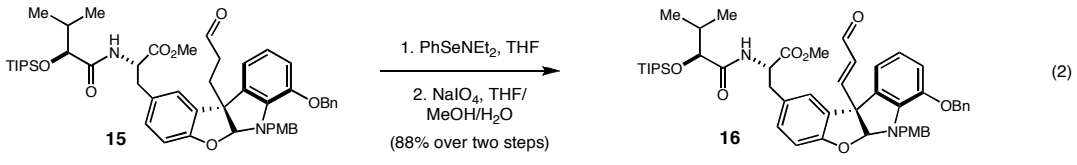
Table 2: Optimization studies on organocatalytic pyrroloindoline formation



Entry	R	HX	Temp	Solvent	dr	Conv
1	Ph	TFA	–78 °C	CH_2Cl_2/MeOH	3:1	85%
2	Ph	TFA	–78 °C	CH_2Cl_2/H_2O	4.3:1	80%
3	N-Bn Indole	TFA	–78 °C	CH_2Cl_2/H_2O	2.8:1	100%
4	Indole	cyanoacetic	–78 °C	CH_2Cl_2/H_2O	1:1	<10%
5	Indole	2,4 DNBA	–40 °C	CH_2Cl_2/H_2O	–	0%
6	indole	TFA	–78 °C	CH_2Cl_2/H_2O	4.7:1	100%
7	indole	TCA	–78 °C	CH_2Cl_2/H_2O	5.8:1	40%
8	indole	PFPA	–78 °C	CH_2Cl_2/H_2O	6:1	40%

Moving from the mixture of CH_2Cl_2 and MeOH to a solution of CH_2Cl_2 and H_2O provided a moderate boost in stereoselectivity while maintaining high levels of reaction efficiency (Table 2, entry 2). This could be further accentuated by use of the *t*-Bu, indole catalyst (Table 2, entry 6). Acid cocatalyst effects are commonly encountered in iminium catalysis and this reaction proved no exception. TFA proved to be the most robust cocatalyst in terms of reactivity, but several similarly acidic co-catalysts afforded slightly higher diastereoselectivities, albeit at the cost of low conversion. Other co-catalysts of similar acidity gave little to no conversion at all (Table 2, entries 4 and 5).

Following furanoindoline formation, the newly formed aldehyde needed to be oxidized to its α,β-unsaturated analogue. Direct oxidation with IBX provided the desired product, though in unacceptably low yield.[13] Rather a two-step oxidation protocol was employed according to the method of Keck (eq 2).[14] Aldehyde **15** was first treated with freshly prepared $PhSeNEt_2$ in THF to yield the α-selenylated aldehyde in quantitative yield. This selenyl functionality was then oxidatively eliminated upon treatment with $NaIO_4$ in $THF/MeOH/H_2O$ to give the desired unsaturated product **16** in 88% yield over two steps. It was also found that this two-step sequence could be carried out in a single reaction flask, but with a slightly diminished isolated yield of 80%.



(2)

Our initial synthetic plan involved functionalizing α,β-unsaturated aldehyde **16** to its corresponding β-hydroxy amino acid. However, all efforts towards these ends met with failure (eq 3). Subjection of **16** to osmium-catalyzed aminohydroxylation and dihydroxylation conditions only returned starting material. Attempts to perform a Weitz-Scheffer-type nucleophilic epoxidation on **16** were also unsuccessful. Presumably, nonbonding interactions between the adjacent bulky quaternary center and the employed reagents are responsible for this conspicuous lack of reactivity.

Faced with this setback we were forced to reexamine our strategy going forward. It occurred to us that the product **17** could also be generated by an aldol reaction between

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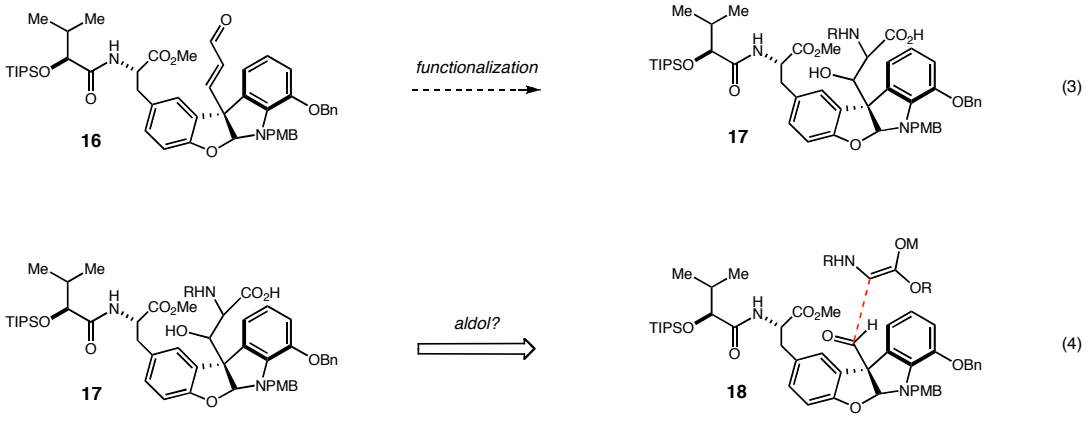
[13] Nicolaou, K. C.; Montagnon, T.; Baran, P. S.; Zhong, Y.-L. *J. Am. Chem. Soc.* **2002**, *124*, 2245–2248.

[14] Keck, G. E.; Cressman, E. N. K.; Enholm, E. J. *J. Org. Chem.* **1989**, *54*, 4345–4349.

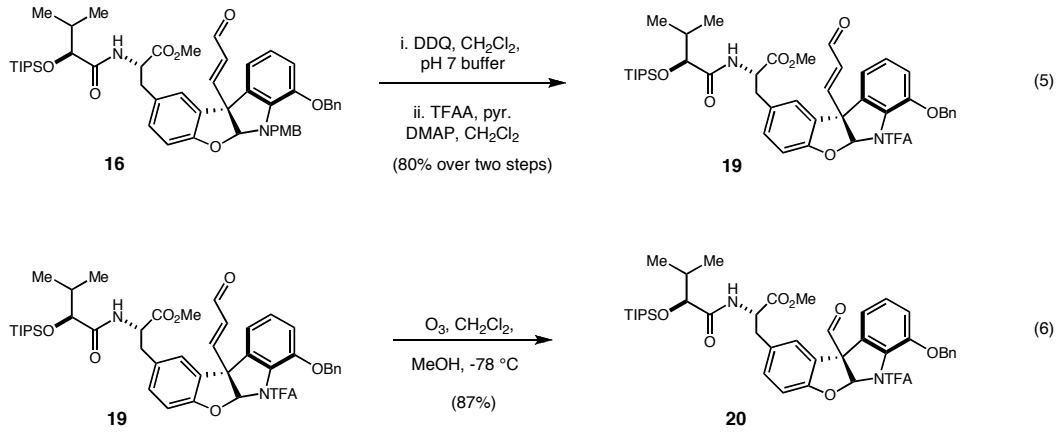
a valine-derived enolate and aldehyde **18**, which in turn could come directly from ozonolysis of **16** (eq 4). While this required the aesthetically undesirable excision of two carbons from the newly installed 3-carbon fragment, this disconnection had the benefit of directly installing the entire C(28)-C(35) chain in a single, highly reliable bond construction.



Towards this end we attempted the direct ozonolysis of **16** and found that oxidation of the electron-rich aminal C-H bond at C(11) was competitive with the desired reaction pathway.[15] We reasoned that this side product could be avoided by making the indoline nitrogen of the aminal core more electron-withdrawn. Accordingly, the indoline PMB protecting group was selectively removed by treatment with DDQ in a biphasic solution of pH 7 buffer and dichloromethane. This relatively unstable product was then immediately reprotected as its trifluoroacetamide after exposure to trifluoroacetic anhydride (TFAA) and DMAP in CH_2Cl_2 to give an 80% yield of **20** over the two steps (eq 5). Remarkably, TFAA was the only reagent found out of many surveyed that was sufficiently electrophilic to acylate the indoline nitrogen. It is important to note that we were prevented from acetylating this nitrogen at an early juncture due to the fact that the

[15] (a) Deslongchamps, P.; Moreau, C.; Frehel, D.; Atlani, P. *Can. J. Chem.* **1972**, *50*, 3402–3404. (b) Deslongchamps, P.; Atlani, P.; Malvalal, A.; Frehel, D.; Moreau, C. *Can. J. Chem.* **1974**, *52*, 3651–3664.

electron-withdrawing trifluoroacetamide would completely diminish the capacity of the parent indole compound to participate in the organocatalytic alkylation of acrolein en route to furanoindoline formation. However, with this protecting group switch secured the ozonolysis of the unsaturated aldehyde **19** was uneventful and gave key aldehyde **20** in 87% yield after reductive workup and column chromatography (eq 6).

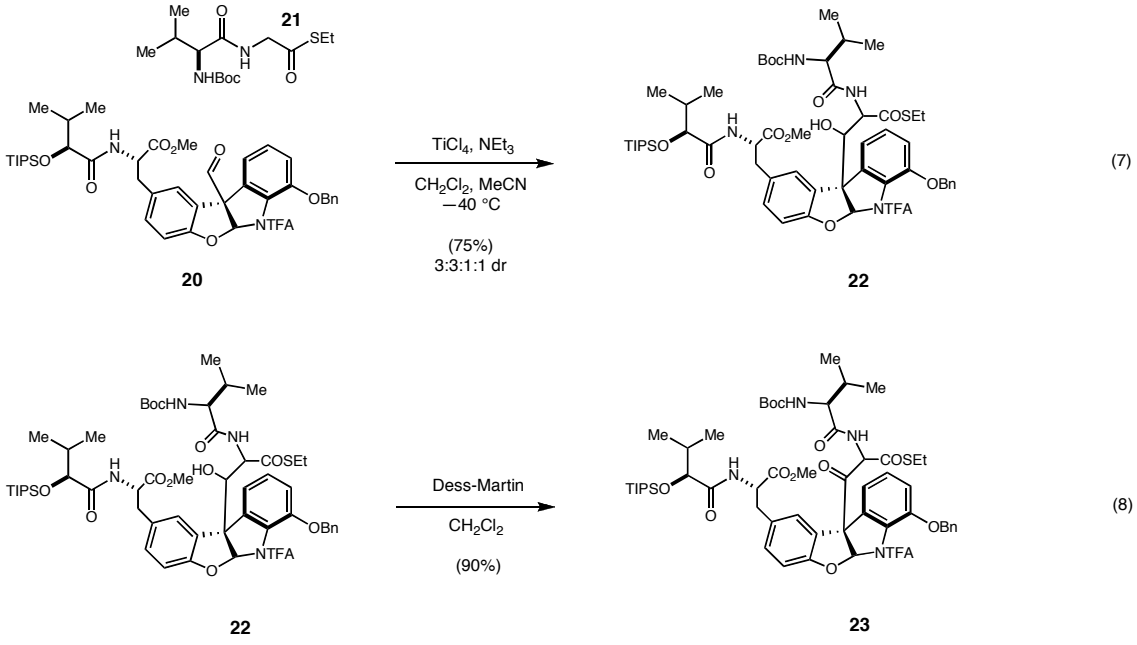


With aldehyde **20** in hand, we were now positioned to investigate our proposed aldol reaction. We were initially concerned that the neopentyl aldehyde electrophile might be difficult for an enolate to engage, but investigations in the MacMillan lab concurrent with this study suggested conditions that might be amenable to use in this difficult case. As part of a program in our laboratories aimed at the three-step asymmetric production of differentially protected amino-carbohydrates, it was found that titanium enolates of valine-derived thioesters were exceptionally effective in reacting with hindered and electronically deactivated aldehyde electrophiles.[16] In this procedure the thioester is complexed at low temperature with titanium tetrachloride, then treated

[16] Kayano, A.; Saliba, K. R.; MacMillan, D. W. C. *Unpublished results*.

triethylamine to effect a soft enolization.[17] Following enolization, acetonitrile is added, followed by the aldehyde and the resulting solution is stirred at –30 °C for 16 hours. Notably, the addition of acetonitrile was found to be critical to obtaining high conversion, presumably by its role of attenuating the Lewis acidity of the titanium center. Application of this protocol to thioester **21** and aldehyde **20** was straightforward and we were delighted to find that, upon optimization, it provided the desired product **22** in 75% yield as a 3:3:1:1 mixture of diastereomers (eq 7). The generation of diastereomers was inconsequential, as they were oxidatively annihilated in a subsequent oxidation with Dess-Martin periodinane to yield ketone product **23** (eq 8).

Scheme 2: Titanium aldol and subsequent oxidation

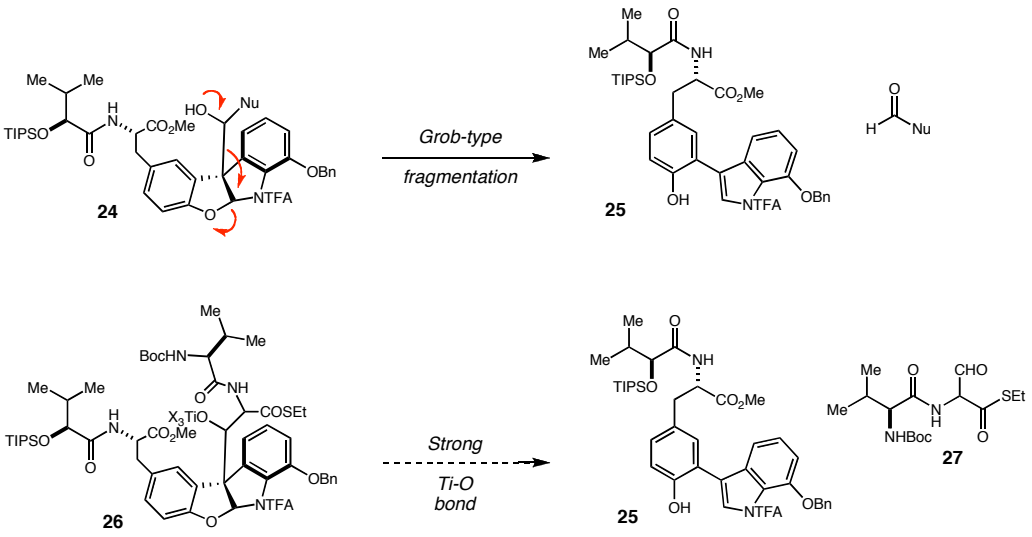


This reaction is all the more remarkable for the fact that treatment of this aldehyde with heteroatom nucleophiles, such as tryptamine or alkaline solutions of methanol,

[17] (a) Harrison, C. R.; *Tetrahedron Lett.* **1987**, *28*, 4135–4138. (b) Annunziata, R.; Cinquini, M.; Cozzi, F.; Borgia, A. L. *J. Org. Chem.* **1992**, *57*, 6339–6342.

results in Grob fragmentation of the furanoindoline core. As shown in Figure 10, this process results in scission of the C(10)-C(30) bond, rearomatization of the indole ring, expulsion of the phenol and transfer of the formyl group to the nucleophile. Presumably, the stability of the metal aldolate intermediate in this case can be attributed to the strength of the titanium(IV)-oxygen bond, which prevents participation in this undesirable and destructive process.[18]

Figure 10: Strength of titanium-oxygen bond precludes Grob fragementation

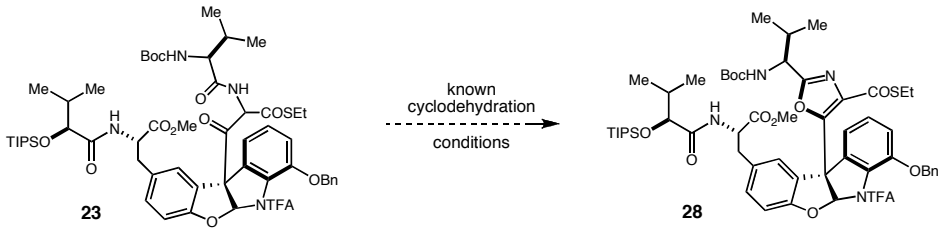


The stage was now set to explore the cyclodehydration of **23** to give the A-ring oxazole of diazonamide A. Classical Robinson-Gabriel dehydration reactions using strong mineral acids resulted in rapid decomposition of the starting material. While the use of $POCl_3$ in pyridine performed admirably in the second Nicolaou synthesis to form the analogous A-ring oxazole, that reagent combination failed to produce any of the

[18] Titanium-oxygen bonds have bond strengths of ~ 100 kcal/mol, while a typical carbon-titanium bond is only ~ 45 kcal/mol. Connor, J. A. *Top. Curr. Chem.* **1977**, *71*, 71.

desired product when applied to substrate **23**.[19] Similarly, the conditions pioneered by Wipf using PPh_3 and C_2Cl_6 also failed to yield any of the desired oxazole product.[20,21] Given the failure of these general and frequently employed oxazole-forming technologies, we were forced to devise a solution that would better suit the reactivity profile of our particularly fragile substrate (Figure 11).

Figure 11: Traditional cyclodehydration methods fail to deliver desired oxazole product



We recognized a mechanistic opportunity to develop a new oxazole-forming protocol based on prior literature involving the nucleophilic fluorinating reagent diethylaminosulfurtrifluoride (DAST). DAST is well known to transform ketones into *gem*-difluorides, through a fluoroacetal-type intermediate **33** (Figure 12).[22] It is proposed that the C-O bond of this intermediate is substantially weakened by coordination by the electrophilic sulfur, making it a highly reactive leaving group that, in the absence of other nucleophiles, can be displaced by fluoride ion to produce the geminal difluorides, such as **34**. Moreover, in 2000, Wipf and coworkers reported the DAST-mediated cyclization of

[19] Nicolaou, K. C.; Hao, J.; Reddy, M. V.; Rao, P. B.; Rassias, G.; Snyder, S. A.; Huang, X.; Chen, D. Y.-K.; Brenzovich, W. E.; Giuseppone, N.; Giannakakou, P.; O'Brate, A. *J. Am. Chem. Soc.* **2004**, *126*, 12897–12906.

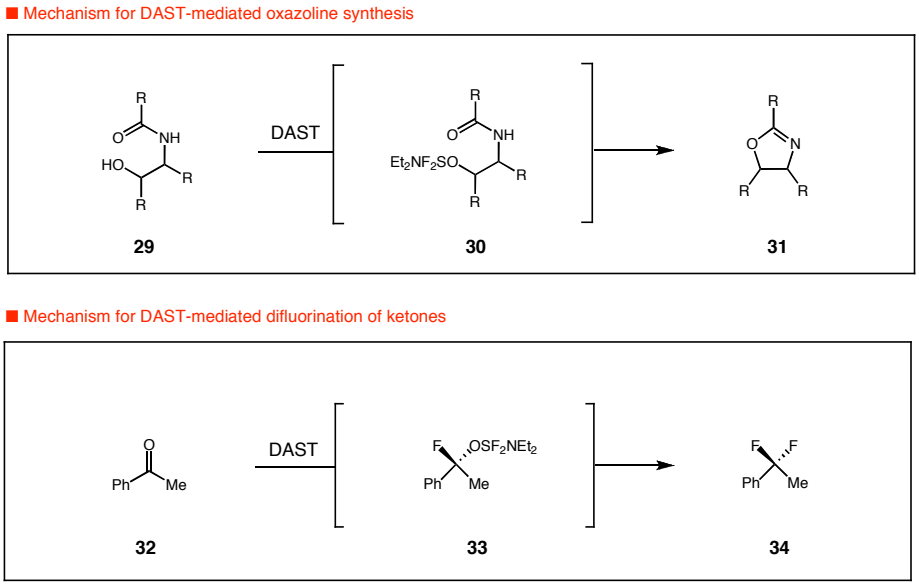
[20] Wipf, P.; Miller, C. P. *J. Org. Chem.* **1993**, *58*, 3604–3606.

[21] A regioisomeric oxazole was isolated from this reaction, arising from the amide carbonyl cyclizing onto the thioester carbonyl rather than the ketone.

[22] (a) Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 575–578. (b) Singh, R. P.; Shreeve, J. M. *Synthesis*, **2002**, *17*, 2561–2578.

amidoalcohols, such as **29**, to form oxazolines such as **31** (Figure 12).[23] In this reaction a DAST leaving group is displaced by intramolecular cyclization of the adjacent amide.

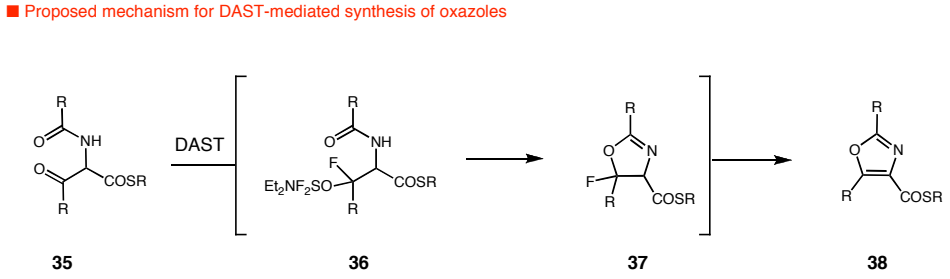
Figure 12: Mechanistic basis for a new oxazole synthesis



We reasoned that if these two known and established mechanisms could be combined, it would form the blueprint of a novel methodology for the synthesis of 4-acyloxazoles, such as we required.

Explicitly, our design plan is illustrated in Figure 13. Treatment of a β-ketoamide such as **35** with DAST would first yield the fluoroacetal **36**. The pendant amide would

Figure 13: Mechanistic proposal for DAST-mediated oxazole synthesis

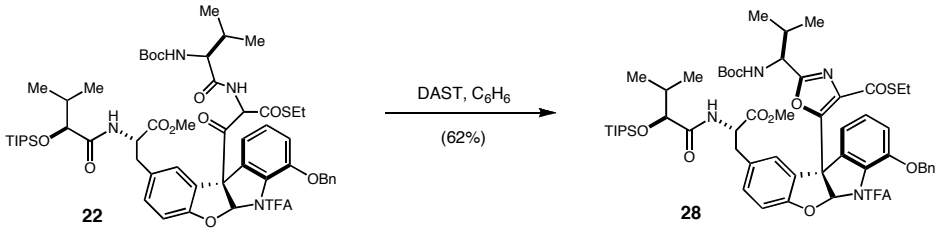


[23] Phillips, A. J.; Uto, Y.; Wipf, P.; Reno, M. J.; Williams, D. R. *Org. Lett.* **2000**, *2*, 1165–1168.

then displace the leaving group in analogy with Wipf's work, yielding an unstable β-fluoro acyloxazoline **37** that should undergo β-elimination to yield the desired oxazole product, **38**.

Gratifyingly, our insight was richly rewarded when we found that exposure of **22** to DAST indeed resulted in formation of the desired oxazole **28** (Scheme 3). Optimization of the reaction conditions proved that non-polar solvents such as benzene and hexanes were superior and yields greater than 65% are routinely observed, even on multigram scale. Notably, no desilylation of the TIPS ether has been observed, despite the production of stoichiometric fluoride ion byproducts. This is the first known instance of DAST being used in the direct construction of oxazoles directly from ketoamides. But given the discussion in the literature of the difficulty encountered in creating this A-ring oxazole and the failure of the more classical methods in this context, it seems promising that these DAST-mediated conditions may prove to be a general method for the creation of trisubstituted 4- acyloxazoles.

Scheme 3: First known use of DAST in the direct synthesis of oxazoles from β-keto amides

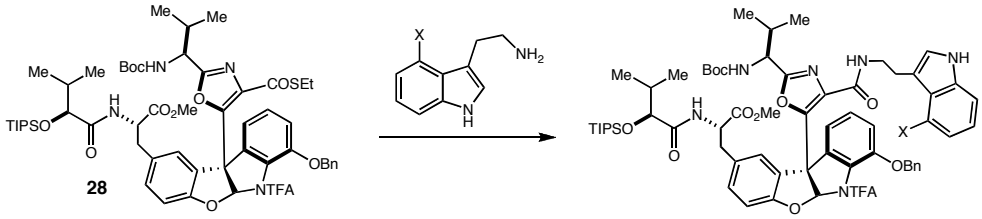


We felt that the successful installation of this central oxazole was a strategically important accomplishment. Firstly, it represented the completion of the intact heterocyclic core of diazonamide A. Secondly, once this oxazole was formed the stability of the aminal core was greatly increased, allowing for more pressing reaction conditions

to be employed than our previous delicate intermediates allowed. Thirdly, this intermediate left many options open in regard to the sequence of steps leading to closure of the two macrocycles. If one route proved untenable then others could easily be assessed from this same point, providing a convenient branch point in exploring downstream chemistry.

From this point the next goal we aimed to achieve was the installation of the B-CD oxazole-indole fragment that constituted the remaining carbons of the diazonamide framework. Towards this end, it would first be necessary to transform the ethyl thioester of **28** into the corresponding tryptamine-derived amide. Initially, it was found that tryptamine displaces the ethyl thioester under DMAP catalysis in toluene at 100 °C to give amide **62** in 33% (Table 3, entry 1). However, all our efforts to optimize this result did not improve upon this unacceptably low yield, and all attempts to introduce more highly functionalized tryptamines met with failure. Fortunately, it was then found that addition of AgTFA to a solution of tryptamine in rigorously degassed MeCN allowed

Table 3: Optimization of thioester aminolysis

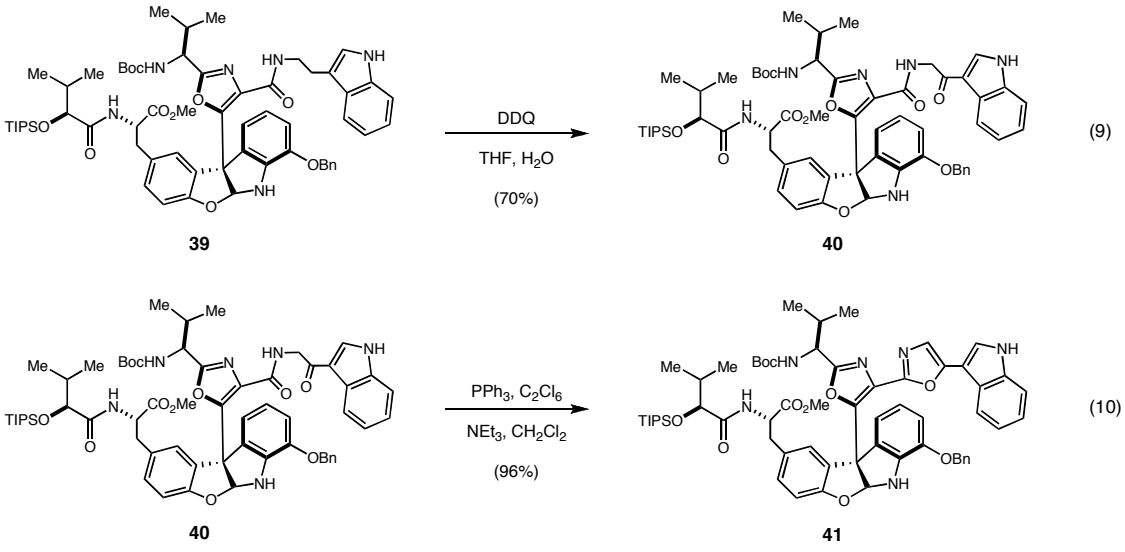


Entry	Activator	X	Temp	Solvent	Time	Yield
1	DMAP	H	100 °C	toluene	24 hr	33%
2	DMAP	Br	100 °C	toluene	–	15%
3	DMAP	Br	100 °C	dioxane	–	<5%
4	AgTFA	H	40 °C	MeCN	1 hr	88%
5	AgTFA	B(pin)	40 °C	MeCN	1 hr	70%

displacement of the thioester in 88% yield after 1 hour at 40 °C (Table 3, entry 4).[24] The mildness of these reaction conditions proved amenable to the incorporation of more complex 4-functionalized tryptamines, including a (pinacolato)boronic ester in the 4-position, which could be envisioned participating in a ring-closing Suzuki reaction to close the right-hand macrocycle (Table 3, entry 5).

Interestingly, exposure of **28** to these conditions and an excess of water in the absence of tryptamine did not produce any of the carboxylic acid but rather returned the unreacted thioester starting material. Moreover, none of the labile trifluoroacetate protecting group was deprotected under these conditions, though in the absence of silver, transamidation of TFA group onto tryptamine in acetonitrile is a rapid and high yielding process. Importantly, the success of this reaction represented successful installation of all the carbons present in the natural product.

Scheme 4: Benzylic oxidation and cyclodehydration towards oxazolyl-indole



39 **40** (9)

40 **41** (10)

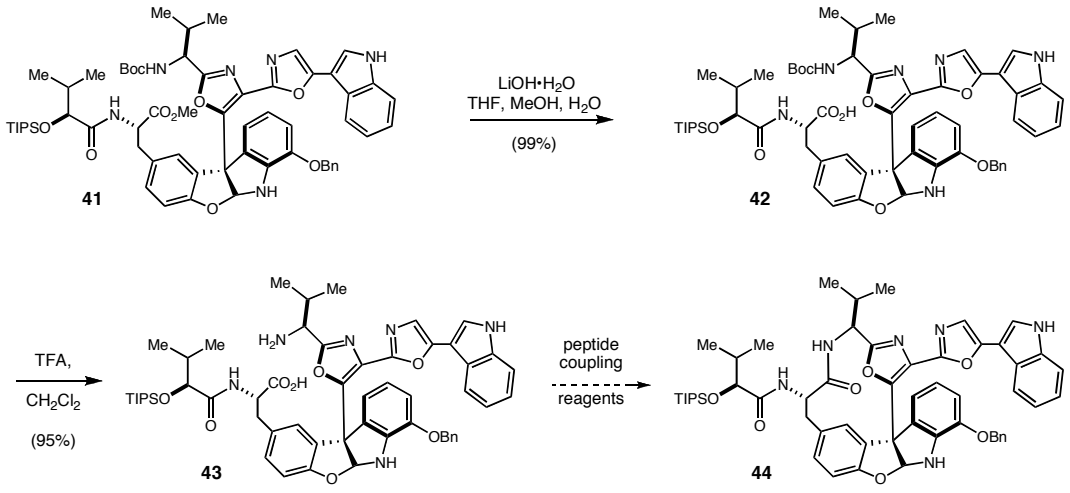
[24] (a) Aggarwal, V. K.; Esquivel-Zamora, B. B. *J. Org Chem.* **2002**, *67*, 8618–8621. (b) Ley, S. V.; Woodward, P. R. *Tetrahedron Lett.* **1987**, *28*, 3019–3020.

Next, tryptamide **39** underwent clean and rapid oxidation at the benzylic position to the 3' ketone after treatment with DDQ in aqueous THF (eq 9).[25] This oxidized adduct **40** was then uneventfully cyclized to bisoxazole compound **41** under the PPh_3/C_2Cl_6 conditions described previously in nearly quantitative yield (eq 10).

With **31** in hand, we felt well situated to explore both macrocyclizations independently, affording numerous possible endgame sequences. Moreover, we were optimistic that successful closure of either of the two twelve-membered rings should aid in the closure of the second by limiting rotation around the C(10)-C(30) bond. Yet, we speculated that the biaryl juncture would be the more difficult one to form, and given the precedence from the Nicolaou and Harran syntheses in successfully closing the right-hand ring once the left-hand ring was in place, we chose first to focus on the closure of the macrolactam.

The substrate for macrolactamization was easily obtained in gram quantities following a high yielding two-step sequence consisting of methyl ester hydrolysis on **41**

Scheme 5: First attempts at macrolactamization

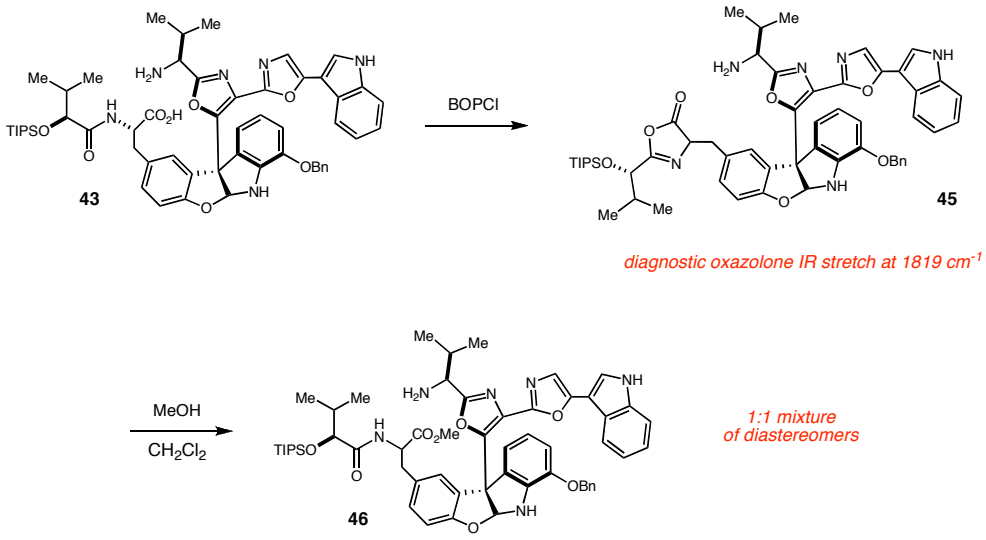


[25] Oikawa, Y.; Yonemitsu, Y. *J. Org. Chem.* **1977**, *42,* 1213–1216.

with lithium hydroxide followed by deprotection of the carbamate **42** with TFA (Scheme 5). However, exposure of the product **43** to a battery of standard peptide coupling reagents provided none of the desired product.[26]

The uronium-based reagents, such as HATU and TBTU, that proved singularly successful in Nicolaou's investigations of an analogous lactamization were completely unsuccessful when applied to **33**. Investigation of even more highly activated reagents, such as PyBrop and BOPCl, led to the isolation of a new non-polar product with the correct molecular mass for the desired product. But, this adduct proved unstable to routine characterization protocols and upon further investigation it proved instead to be the oxazolone **35** resulting from intramolecular attack of the adjacent valeric amide carbonyl onto the activated carboxylate. This oxazolone was characterized in part by the diagnostic IR signature of this functionality at 1819 cm^{-1} and the observation that treatment of this adduct with methanol in dichloromethane returned the

Scheme 6: Undesired oxazolone formation

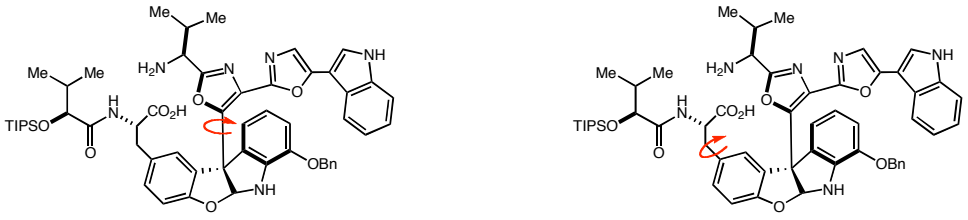


[26] For reviews on various aspects of macrolactamization and large ring synthesis, see: (a) Li, P.; Roller, P. P.; Xu, J. *Current Organic Chemistry*, **2002**, *6*, 411–440. (b) Roxburgh, C. *Tetrahedron* **1995**, *51*, 9767–9822.

methyl ester **46** in quantitative yield as a 1:1 mixture of epimers at the α-amino stereocenter.

We were curious if hindered rotation about the C(10)-C(30) and C(3)-C(4) axes might be precluding the desired bond-forming event by effectively locking the substrate into unreactive rotameric conformations wherein the amine and the activated carboxylate are held distal to one another. However, molecular mechanics simulations indicated that the activation barrier for rotation around the C(10)-C(30) dihedral was only 8.08 kcal/mol, meaning the compound was rotating around this axis an average of 13 million times a second at room temperature (Figure 14).[27] Similarly, the barrier to rotation about the C(3)-C(4) bond was only 7.47 kcal/mol, according nearly 40 million rotations per second. Thus, the possibility of a rotameric bias in adopting a reactive conformation for ring-closure was disregarded.

Figure 14: Relevant rotational barriers in macrolactamization



E_a = 8.08 kcal/mol
$k_{rot} = 1.3 \times 10^7\ sec^{-1}$

E_a = 7.47 kcal/mol
$k_{rot} = 3.9 \times 10^7\ sec^{-1}$

Thus faced with the failure of our efforts to affect a viable macrolactamization on **43**, we opted instead to begin exploration of chemistry to form the right-hand ring biaryl. We hypothesized that a number of different transformations could provide the desired

[27] These MM3 calculations were carried out using Macromodel. Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskcamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440–467.

product, such as Suzuki or Stille couplings, aryl Heck-type chemistry, Witkop photocoupling, or oxidative biaryl coupling. Yet given the advanced nature of our intermediates and the seemingly clear correspondence to prior work in the field, we decided to first investigate the use of the Witkop-type chemistry that had previously been successfully applied by Harran and Nicolaou.[28]

Yet for all the apparent similarities, it was unclear if such a process would be viable in our circumstances. The most worrisome question was whether the aryl triflate would be able to accept an electron from the pendant photo-excited indole and undergo efficient fragmentation to yield the requisite aryl radical. We could find no literature precedent for carrying out Witkop cyclizations employing triflates and all the previous examples in the diazonamide field had used aryl bromides.[29] Moreover, triflates are known to be somewhat photo-labile, and if the rate of electron transfer and subsequent ring closure was too slow, then competitive hydrolysis pathways may consume the starting material.

The substrate was prepared in a straightforward manner by hydrogenolysis of the benzyl ether **41**, followed by reprotection of the resulting phenol as its corresponding triflate **47** (Scheme 7). We then found, after substantial optimization, that when **47** was irradiated for one hour with 356 nm light in a solution of aqueous acetonitrile and potassium phosphate, the desired product **49** could be obtained in 38% yield with 30% recovered **47** (54% based on recovered starting material). Though the yield of the reaction was modest, it was in line with that reported with the corresponding bromide in

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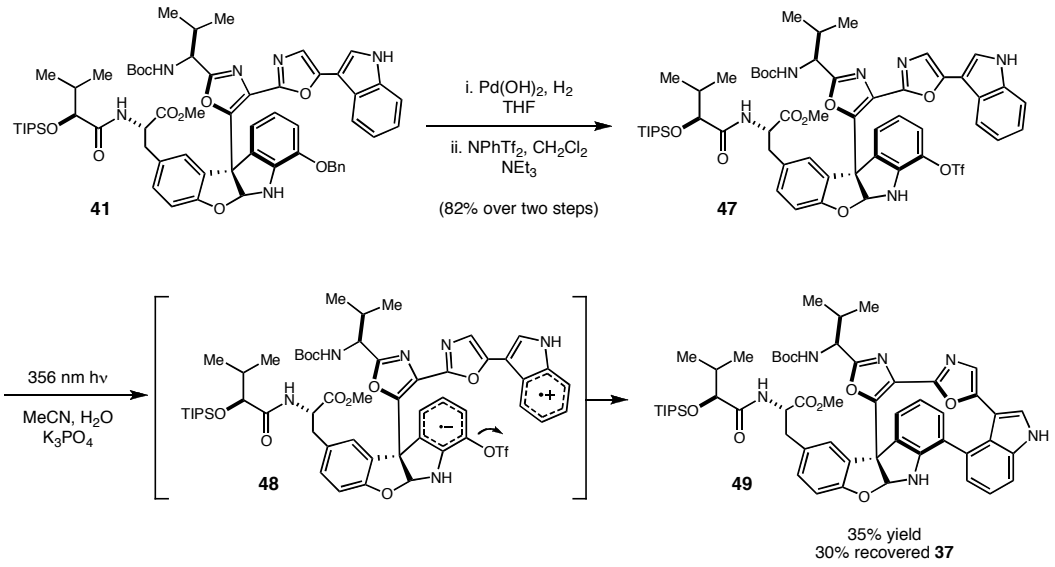
[28] For a detailed discussion of this step in these prior syntheses, see Chapter 2.

[29] The use of a 7-oxy substituted indole was necessary to achieve high levels of reactivity in the organocatalytic addition/cyclization. The analogous reaction using the 7-bromoindole derivatives was nonproductive.

the Nicolaou synthesis. Efforts to optimize the reaction efficiency further were hampered by the discovery that the product itself was not indefinitely stable to the reaction conditions, and to obtain the highest yields the reaction had to be stopped well short of full conversion of starting material.[30] Notably, however, the phenol resulting from triflate hydrolysis was not detected as a component of the reaction mixture.

Scheme 7: Photocyclization of the right-hand macrocycle

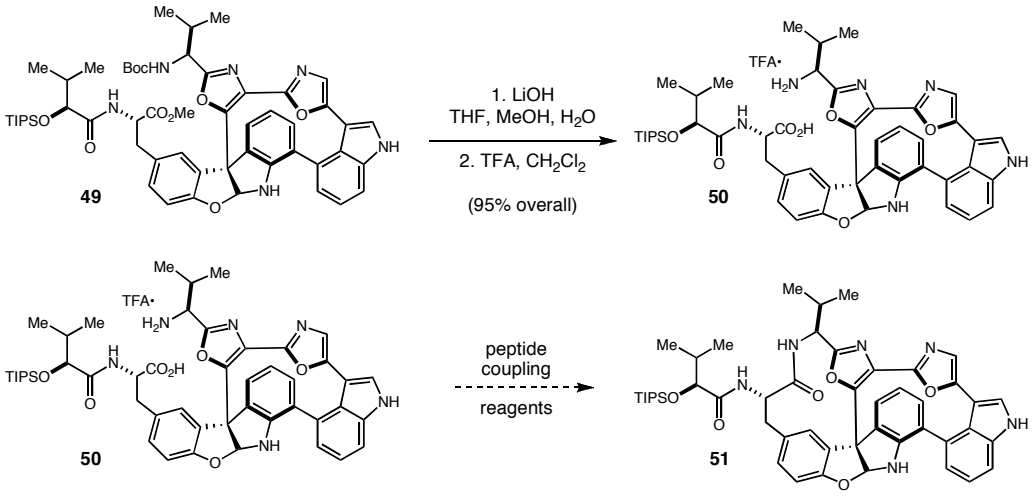


With this result in hand, we again turned our attention to the closure of the left-hand macrolactam. Notably, if this lactamization could be realized, the only steps necessary to complete the total synthesis of diazonamide A would be the known chlorination of the B-ring oxazole and D-ring indole and deprotection of the silyl ether. Moreover, we were optimistic that the increased structural rigidity of **49** would substantially aid the chances of now successfully carrying out the desired amide-forming event. The same two-step deprotection sequence was employed again to transform **49**

[30] The efficiency of this reaction suffered when the reactions were run on scales larger than 5 mg. Yet, running many scale reactions simultaneously in the photoreactor allowed for sufficient throughput of material.

into **50** (Scheme 8). However, much to our consternation, all of our efforts to cyclize **50** met with failure. All reagents surveyed only returned mixtures of starting material, oxazolone, dimer, and higher-order oligomers.

Scheme 8: Failed macrolactamization redux



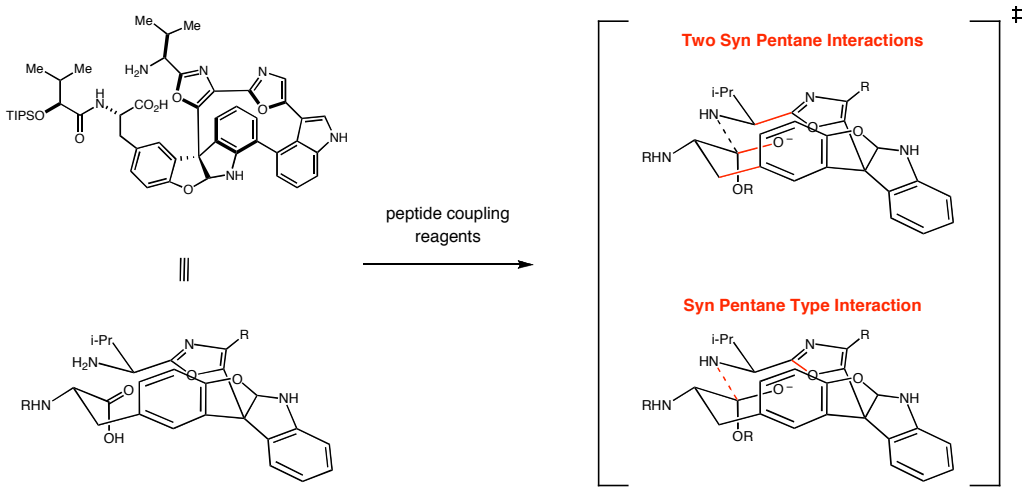
This result was confounding for a number of reasons. DFT calculations indicated that the ring closure of the amino-acid chloride with expulsion of HCl was exothermic by 6.9 kcal/mol.[31] Thus the reaction was not failing on thermodynamic grounds. Yet, arguments supporting failure of the reaction on kinetic grounds seemed counterintuitive. Intermolecular coupling of the carboxylic acid of **50** to tryptamine proceeded efficiently. Thus the problem did not reside in the formation of the activated carboxylate. Moreover, due to the rigidity of the structure, the reactive ends of the chain are held very close together in space, with ample degrees of freedom to align in a bonding-type orientation.

The best explanation for the failure of this late-stage that we can posit comes from examining the nonbonded interactions introduced into the macrocycle during the initial C-N bond forming event. Analysis of the tetrahedral intermediate reveals that upon

[31] Calculated (B3LYP 3-21G) using the corresponding acid chloride. For details, see supporting information.

achieving bond C-N formation, three new s*yn*-pentane type interactions are fully developed (Figure 15). Each of these nonbonded interactions is worth several kcal/mol in the ground state, and likely substantially more in the transition state.[32] As such we believed that, due to the high energetic penalty associated with assuming a conformation containing these new *syn*-pentane interactions, that the kinetic barrier to form the tetrahedral intermediate is simply too high to be overcome.

Figure 15: Rationale for failure of macrolactamization



■ Kinetic barrier to acheiving tetrahedral intermediate becomes insurmountable

In light of this rationalization, we realized that our synthetic route had a serious and irredeemable strategic flaw. We would have to devise a substantially different approach to the left-hand macrocycle in order to have any hope of achieving a completed total synthesis. Our efforts towards these ends are presented in the subsequent chapters.

[32] Energetic penalties associated with torsional interactions are much greater in transition states than they are in ground states: Caramella, P.; Rondan, N. G.; Paddon-Row, M. N.; Houk, K. N. *J. Am. Chem. Soc.* **1981**, *103*, 2438–2440.

Chapter 3 Supporting Information

General Information: Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[33] All solvents were purified according to the method of Grubbs.[34] Nonaqueous reagents were transferred under argon via syringe or cannula. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator using a heated water bath. Chromatographic purification of products was accomplished using forced-flow chromatography on Silicycle 230–400 mesh silica gel 60 according to the method of Still.[35] Thin-layer chromatography (TLC) was performed on Silicycle 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by fluorescence quenching or by CAM stain.

^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 (300 MHz and 75 MHz) as noted, and are internally referenced to residual solvent signals. Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (Hz), and assignment. Data for ^{13}C NMR are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer 1000 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Mass spectra were obtained from the Caltech Mass Spectral Facility.

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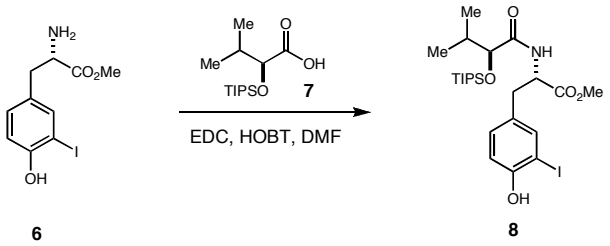
[33] Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals;* 3rd ed., Pergamon Press, Oxford, 1988.

[34] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.

[35] Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978**, *43*, 2923.

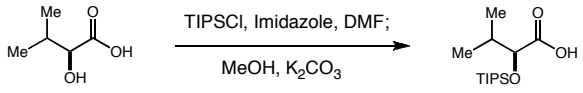
Optical rotations were measured on a Jasco P-1010 polarimeter, and $[\alpha]_D$ values are reported in 10^{-1} dg cm^2 g^{-1}.[36]



Iodophenol 8: Amine **6** (15.4 g, 47.95 mmol), acid **7** (11.96 g, 43.59 mmol), EDC (9.19 g, 47.95 mmol), and HOBT (6.47 g, 47.95 mmol) are combined in a 500 mL round bottom flask and 190 mL of DMF is added. After 12 hours the reaction mixture is diluted with 500 mL of ether and washed with 3 x 500 mL of water. The combined organic fractions are washed with brine and concentrated. The resulting oil is purified on silica gel (30% ethyl acetate in hexanes) to yield the title compound as a colorless oil (21.2 g, 82% yield). IR (Film): 3402, 2944, 2867, 1746, 1654, 1603, 1505, 1462, 1415, 1347, 1292, 1215, 1099, 1058, 882, 822, 684 cm^{-1}; ^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.44 (d, 1H, J = 2.1 Hz, Ar**H** ortho to iodide), 7.05 (br s, 1H, N**H**), 6.99 (dd, 1H, J = 2.1, 8.55 Hz, Ar**H** para to iodide), 6.87 (d, 1H, J = 8.5 Hz, Ar**H** meta to iodide), 5.82 (s, 1H, O**H**), 4.87 (m, 1H, NH**CH**), 4.15 (d, 1H, J = 3.3 Hz, C**H**OTIPS), 3.69 (s, 3H, CO_2**Me**), 2.91 (m, 2H, ArC**H$_2$**), 1.99 (m, 1H, C**H**$(CH_3)_2$), 1.1–1.0 (m, 21H, TIPS), 0.93 (d, 3H, J = 7.2 Hz, CH(C**H$_3$**)$_2$), 0.861 (d, 3H, J = 7.2 Hz, CH(C**H$_3$**)$_2$), ^{13}C NMR: (75 MHz, $CDCl_3$) δ

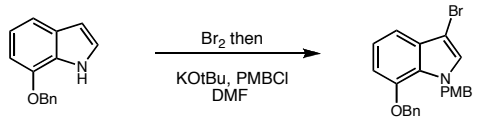
[36] Certain data herein was reproduced from the Caltech thesis of Ian K. Mangion, (2006) with whom this work was jointly carried out.

172.88, 171.6, 154.5, 139.2, 131.0, 130.0, 115.3, 85.6, 78.3, 52.6, 52.4, 37.4, 34.2, 18.2, 18.1, 17.9, 17.5, 12.6 HRMS (FAB+) exact mass calculated for [M+H] ($C_{24}H_{41}NO_5SiI$) requires *m/z* 578.1799, found *m/z* 578.1791; $[\alpha]_D^{25} = -5.75$ (c = 1.0 $CHCl_3$).



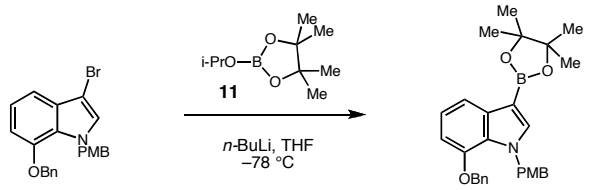
7

TIPS hydroxy valeric acid 7: To (*S*)-2-hydroxy valeric acid (5.0 g, 42.3 mmol) in a stirred solution of DMF (22 mL) was added triisopropylsilyl chloride (22 mL, 102 mmol) and imidazole (1.38 g, 204 mmol). After 24 hours, MeOH (210 mL) and 1M aqueous K_2CO_3 (64 mL) were added to this slurry, and after 4 h the resultant solution was diluted with 400 mL H_2O, acidified to pH 4, and extracted 3 x 300 mL with EtOAc. The combined organic fractions are washed with brine and concentrated. The resulting oil is purified of remaining TIPSOH by vacuum distillation of this impurity (85 °C, min. 10 mTorr) to yield the title compound as a colorless oil (9.7 g, 82% yield). IR (Film): 2963, 2945, 2869, 1723, 1465, 1388, 1234, 1152, 1068, 997, 882, 825, 681 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ 4.26 (d, 1H, J = 3.6 Hz, C**H**OTIPS), 2.06 (m, 1H, C**H**$(CH_3)_2$), 1.10–0.97 (m, 27H, TIPS, CH(C**H**$_3)_2$), ^{13}C NMR: (75 MHz, $CDCl_3$) δ 173.2, 65.9, 33.7, 17.9, 17.8, 17.7, 17.0, 15.3, 12.2; HRMS (FAB+) exact mass calculated for [M+H] ($C_{14}H_{31}O_3Si$) requires *m/z* 275.2043, found *m/z* 275.2041; $[\alpha]_D^{25} = -16.81$ (c = 1.0 $CHCl_3$).

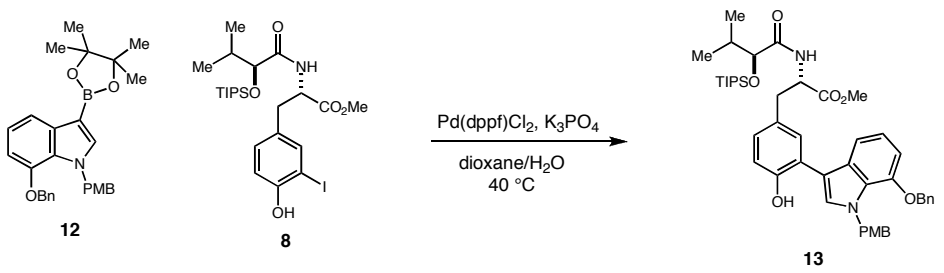


9 **10**

Bromoindole 10: To a room temperature solution of 7-benzyloxyindole **9** (5.0 g, 22.4 mmol) in 90 mL of DMF was added bromine (1.18 mL, 22.84 mmol) dropwise over the course of ten minutes. After 20 minutes the solution was cooled to 0 °C and KOtBu (5.78 g, 51.5 mmol) was added in a single portion. 30 minutes later PMBCl (3.65 mL, 26.88 mmol) was added dropwise over several minutes by syringe, after which the reaction mixture was allowed to warm to room temperature. After 6 hours the reaction was judged complete by TLC and the reaction mixture was diluted with 300 mL of diethyl ether and washed with 100 mL of 1% $Na_2S_2O_3$. The organic portions were washed three times with water and then once with brine before being dried over sodium sulfate. The organic portion was then concentrated *in vacuo* to yield a viscous yellow oil. These crude extracts could then be recrystallized from a hot mixture of 10% ethyl acetate in hexanes to afford 7.27 g (77%) of the title compound as a white crystalline solid. IR (Film): 2931, 1611, 1574, 1512, 1497, 1453, 1422, 1383, 1322, 1248, 1209, 1175, 1080, 1056, 1033, 988, 875, 818, 774, 727, 695, 625 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ 7.38–7.25 (m, 5H, Ar**H**s), 7.19 (dd, 1H, J = 0.9, 7.8 Hz, Ar**H**), 7.07 (t, 1H, J = 7.8 Hz, Ar**H**), 7.04 (s, 1H, C(2)-**H**), 6.95–6.88 (m, 2H, Ar**H**), 6.80–6.72 (m, 3H, Ar**H**), 5.51 (s, 2H, PhC**H**$_2$), 5.12 (s, 2H, PMBC**H**$_2$), 3.77 (s, 3H, **Me**O-Ar) ^{13}C NMR: (300 MHz, $CDCl_3$) δ 158.9, 146.6, 136.7, 130.9, 129.9, 128.6, 128.1, 127.8, 125.7, 120.8, 114.0, 112.3, 104.6, 90.4, 70.5, 55.3, 52.2 HRMS (EI+) exact mass calculated for [M+•] ($C_{23}H_{20}NO_2Br$) requires *m/z* 421.0677, found *m/z* 421.0672.

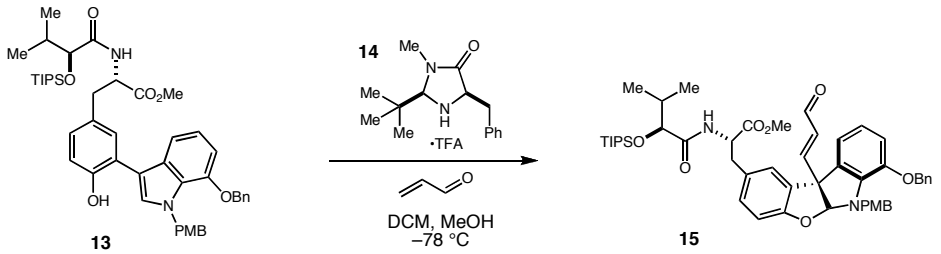


Indole Boronic Ester 12: To a solution of *n*-butyllithium (7.34 mL, 10.65 mmol, 1.2 eq, 1.45M in hexanes) in 80 mL of THF at –78 °C was added bromoindole **10** (3.75 g, 8.88 mmol, 1.0 eq) in 10 mL of THF dropwise via syringe over 10 minutes. After 15 minutes, freshly distilled 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **11** (3.62 mL, 17.76 mmol, 2.0 eq) was added via syringe. This reaction mixture was allowed to warm to ambient temperature over 3 hours. At this point, 100 mL of a saturated aqueous solution of NH_4Cl was added to the reaction mixture and the layers were separated. The aqueous layer was washed 3 x 100 mL with EtOAc. The combined organic layer was washed with 100 mL of brine, dried over sodium sulfate, and concentrated *in vacuo*. The residual oil was then recrystallized from a hot solution of 10% EtOAc in hexanes to give the title compound as an off-white crystalline solid (3.40 g, 82% yield). The remaining mass was recovered as debrominated **10**. IR (Film): 2976, 1613, 1573, 1539, 1513, 1495, 1454, 1379, 1290, 1267, 1247, 1206, 1144, 1107, 1059, 1009, 783, 735, 696, 681 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ 7.66 (dd, 1H, J = 0.6, 8.1 Hz, Ar**H**), 7.48 (s, 1H, C(2)-**H**), 7.35–7.22 (m, 5H, Ar**H**), 7.03 (t, 1H, J = 8.1Hz, Ar**H**), 6.91–6.87 (m, 2H, Ar**H**), 6.78–6.65 (m, 3H, Ar**H**), 5.52 (s, 2H, PhC$\mathbf{H}_2$), 5.09 (s, 2H, PMBC$\mathbf{H}_2$), 3.75 (s, 3H, **Me**O-Ar), 1.35 (s, 12H, 4x**Me**) ^{13}C NMR: (300 MHz, $CDCl_3$) δ 158.7, 146.6, 138.8, 137.0, 135.3, 131.3, 128.5, 128.4, 128.1, 127.9, 127.8, 126.9, 120.8, 115.7, 113.8, 104.1, 82.8, 70.3, 55.3, 52.2, 25.0 HRMS (EI+) exact mass calculated for [M+•] ($C_{29}H_{32}BNO_4$) requires *m/z* 469.2424, found *m/z* 469.2416.



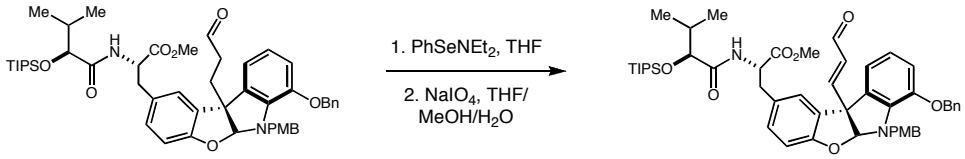
Phenol 13: A 100 mL round bottom flask with stirbar is charged with $Pd(dppf)Cl_2$ (0.633 g, 0.7755 mmol), K_3PO_4 (8.78 g, 41.36 mmol) and indole boronic ester **12** (8.74 g, 18.62 mmol) in a glove box. This flask was capped with a rubber septa and brought out of the box where in it was placed under a balloon of argon. To the flask is added aryl iodide **8** (5.976 g, 10.34 mmol) in a 60 mL of degassed 1,4-dioxane. To this solution is then added 6 mL of degassed water and the resulting solution is stirred at 40 °C for 2 hours. After the reaction was judged complete by TLC analysis, the reaction mixture was diluted with 200 mL of diethyl ether and washed sequentially with 100 mL portions of water, saturated NH_4Cl solution, and brine. The organic portion is dried over sodium sulfate and concentrated *in vacuo*. These crude extracts were purified by column chromatography (4% Et_2O/CH_2Cl_2) to yield the title compound (6.38 g, 78%) as a white amorphous solid. IR (Film): 3409, 2945, 2867, 2360, 1747, 1654, 1612, 1570, 1512, 1456, 1385, 1248, 1209, 1175, 1063, 882, 821 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ 7.34–6.68 (m, 17H, Ar**H** and N**H**); 5.59 (s, 2H, OC**H**$_2$Ph), 5.34 (s, 1H, ArO**H**), 5.15 (s, 2H, OC**H**$_2$-pMeOPh), 4.90 (ddd, 1H, J = 6.0, 6.3 and 8.4 Hz, C**H**CO_2Me), 4.14 (d, 1H, J = 3.3 Hz, C**H**OTIPS); 3.77 (s, 3H, ArO**Me**); 3.66 (s, 3H, CO_2**Me**); 3.05 (m, 2H, *C***H**$_2$Ar); 1.93 (ddq, 1H, J = 3.6, 7.2, and 7.9 Hz, C**H**Me_2); 1.10–0.98 (m, 21H, TIPS); 0.88 (d, 3H, J = 6.9 Hz, CH(**Me**)Me); 0.79 (d, 3H, J = 6.9 Hz, CH(**Me**)Me) ^{13}C NMR: (300 MHz, $CDCl_3$) δ 172.4, 171.8, 158.8, 152.5, 146.9, 136.7, 131.0, 129.2, 129.1, 128.6, 128.1, 128.0, 127.8,

127.5, 126.5, 121.1, 120.9, 115.4, 113.9, 112.7, 110.9, 104.6, 78.1, 76.6, 70.4, 55.2, 52.5, 52.2, 52.1, 37.7, 33.9, 18.0, 17.9, 17.7, 17.2, 12.3; HRMS (FAB+) exact mass calculated for [M+•] ($C_{47}H_{60}N_2O_7Si$) requires *m/z* 792.4170, found *m/z* 792.4175; $[\alpha]_D^{25}$: –9.39 (c = 1.03, $CHCl_3$).



Aldehyde 15: (2*R*,5*R*)-2-*tert*-butyl-5-benzyl-3-methylimidazolidin-4-one•TFA **14** (0.313 g, 0.87 mmol) and phenol **13** (2.30 g, 2.90 mmol) are dissolved in 13.75 mL of dichloromethane and 0.75 mL of MeOH. This mixture is cooled to –78 °C. To this cold solution is added freshly distilled acrolein (1.94 mL, 29.0 mmol) at –78 °C. The reaction is left at –78 °C for 48 hours before being diluted with 25 mL of pH 7 buffer. The layers were separated and the organic portions were washed with brine and dried over sodium sulfate. Following concentration *in vacuo*, the crude reaction extracts were purified by flash chromatography in 12:3:1 ratio of dichloromethane, hexanes, and diethyl ether to afford the title compound as an amorphous white solid (1.92 g, 85%) in a 3.5:1.0 mixture of diastereomers at the C(10) stereocenter. IR (film): 3415, 2944, 2866, 1743, 1677, 1611, 1511, 1494, 1464, 1365, 1247, 1174, 1098, 882, 821, 734, 684 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) 9.49 (s, 1H, C**H**O), 7.33–6.68 (m, 12H, Ar**H** and N**H**); 5.82 (s, 1H, OC**H**N), 5.29 (d, 1H, J = 15.3 Hz, NCH(**H**)Ar), 5.02 (d, 2H, J = 5.7 Hz, OC$\mathbf{H_2}$Ph), 4.88

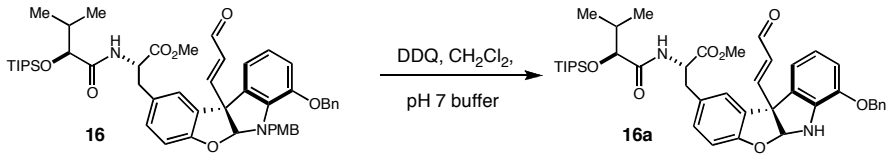
(m, 1H, NHC**H**), 4.49 (d, 1H, J = 15.3 Hz, NCH(**H**)Ar), 4.12 (d, 1H, J = 3.6 Hz, C**H**OTIPS); 3.78 (s, 3H, ArO**Me**); 3.61 (s, 3H, CO_2**Me**); 3.01 (m, 2H, **CH_2**Ar); 2.15–1.80 (m, 5H, CHOC**H_2CH_2** and C**H**$(CH_3)_2$), 1.10–0.95 (m, 21H, TIPS); 0.88 (d, 3H, J = 7.2 Hz, CH(**Me**)Me); 0.79 (d, 3H, J = 7.2 Hz, CH(Me)**Me**) ^{13}C NMR: (75 MHz, $CDCl_3$) δ 200.6, 172.3, 171.7, 158.8, 157.8, 144.4, 137.1, 136.8, 133.5, 131.9, 130.9, 129.5, 129.4, 128.5, 128.4, 127.9, 127.5, 123.7, 120.2, 115.7, 113.9, 113.4, 109.8, 105.8, 78.1, 70.9, 68.0, 57.9, 55.2, 52.6, 52.1, 50.4, 39.0, 38.1, 33.9, 29.2, 25.6, 18.0, 17.91, 17.87, 17.7, 17.3, 12.3 HRMS: (FAB+) exact mass calculated for [M+H] ($C_{50}H_{65}N_2O_8Si$) requires *m/z* 849.4354, found *m/z* 849.4386.



15 **16**

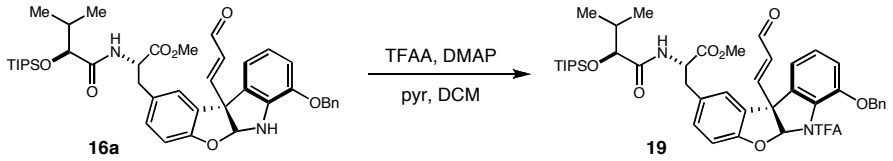
Aldehyde 16: To a solution of aldehyde **15** (6.1 g, 7.184 mmol) in 36 mL of dichloromethane at room temperature was added $PhSeNEt_2$ (1.80 mL, 9.34 mmol). After stirring for one hour the reaction was judged complete by TLC. The reaction mixture was concentrated *in vacuo* and the crude extracts were purified by flash chromatography (33% ethyl acetate in hexanes). The product was thus obtained as a yellow oil in a 3:3:1:1 mixture of diastereomers as judged by ^{1}H NMR. This product was then taken up in 60 mL of THF, 30 mL of methanol, and 30 mL of water and cooled to 0 °C. To this cold solution was added sodium periodate (7.21 g, 7.184 mmol) in a single portion. After 24 hours the reaction mixture was concentrated *in vacuo* to remove the methanol and THF,

diluted with ethyl acetate, and washed with water. After separation of the layers the organic portions were washed with brine and dried over sodium sulfate. Concentration of the resulting solution gave a yellow oil which could be purified by column chromatography (20%–35% ethyl acetate in hexanes) to give the title compound as an amorphous off-white solid (5.63 g, 88%). IR (Film): 3414, 2945, 2867, 2360, 1743, 1690, 1611, 1511, 1494, 1464, 1365, 1248, 1176, 1100, 882, 822, 749, 684 cm^{-1}; ^{1}H NMR: (300 MHz, $CDCl_3$) 9.45 (d, 1H, J = 7.5 Hz, C**H**O), 7.40–6.68 (m, 17H, Ar**H,** CHOCH=C**H** and N**H**); 5.97 (s, 1H, OC**H**N), 5.88 (dd, 1H, J = 7.8 and 15.6 Hz, CHOC**H**=CH) 5.23 (d, 1H, J = 15 Hz, NCH(**H**)Ar), 5.02 (d, 2H, J = 1.5 Hz, OC$\mathbf{H_2}$Ph), 4.89 (m, 1H, NHC**H**), 4.49 (d, 1H, J = 15 Hz, NCH(**H**)Ar), 4.12 (d, 1H, J = 3.3 Hz, C**H**OTIPS); 3.76 (s, 3H, ArO**Me**); 3.61 (s, 3H, CO_2**Me**); 3.02 (m, 2H, **C**$\mathbf{H_2}$Ar); 2.0–1.80 (m, 1H, C**H**$(CH_3)_2$), 1.10–0.95 (m, 21H, TIPS); 0.88 (d, 3H, J = 7.2 Hz, CH(**Me**)Me); 0.78 (d, 3H, J = 7.2 Hz, CH(Me)**Me**) ^{13}C NMR: (75 MHz, $CDCl_3$) δ 192.7, 172.3, 171.6, 158.9, 158.1, 154.9, 145.4, 137.4, 136.6, 133.1, 131.7, 130.3, 130.2, 129.7, 129.6, 129.2, 128.8, 128.5, 128.0, 127.5, 127.0, 124.8, 121.2, 117.0, 113.9, 113.7, 110.1, 106.8, 78.1, 77.2, 70.8, 61.6, 55.2, 52.7, 52.4, 52.1, 51.2, 38.0, 33.9, 21.0, 18.0, 17.91, 17.87, 17.7, 17.2, 14.2, 12.3 HRMS: (FAB+) exact mass calculated for [M+H] ($C_{50}H_{63}N_2O_8Si$) requires *m/z* 847.4354, found *m/z* 847.4313; $[\alpha]_D^{25} = -37.11$ (c = 1.0 $CHCl_3$).



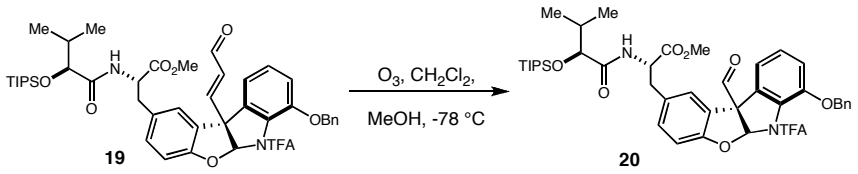
Aldehyde 16a: To a vigorously stirred solution of aldehyde **16** (810 mg, 0.956 mmol) in a 1:1 mixture of dichloromethane and pH 7 buffer (16 mL each) at 0 °C was added freshly recrystallized DDQ (477 mg, 2.10 mmol). The resulting dark green heterogeneous reaction mixture is allowed to warm to ambient temperature over the course of two hours, after which time it is diluted with 100 mL of ethyl acetate and washed with 100 mL of a saturated solution of sodium bicarbonate. The layers were separated and the aqueous layer was washed three times with 50 mL of ethyl acetate. The combined organic layer was washed with brine and dried over sodium sulfate. Purification by flash chromatography on iatrobeads (25%–35% ethyl acetate in hexanes) gave the desired product as an amorphous off-white solid as a 3.5:1 mixture of diastereomers in 89% yield (620 mg). IR (film): 3413, 2945, 2867, 1743, 1689, 1620, 1497, 1464, 1348, 1250, 1207, 1098, 1057, 882, 822, 737, 684 cm^{-1}; ^{1}H NMR: (300 MHz, $CDCl_3$) 9.62 (d, 1H, J = 7.8 Hz, C**H**O), 7.40–6.68 (m, 12H, Ar**H,** CHOCH=C**H** and CON**H**); 6.27 (s, 1H, OC**H**N), 6.18 (dd, 1H, J = 7.8 and 16.2 Hz, C**H**OCH=CH), 5.13 (br s, 1H, OCHN**H**) 5.05 (s, 2H, OC$\mathbf{H}_2$Ph), 4.91 (m, 1H, CONHC**H**), 4.13 (d, 1H, J = 3.6 Hz, C**H**OTIPS); 3.62 (s, 3H, CO_2**Me**); 3.04 (m, 2H, **C**$\mathbf{H}_2$Ar); 2.00–1.85 (m, 1H, C**H**$(CH_3)_2$), 1.10–0.95 (m, 21H, TIPS); 0.89 (d, 3H, J = 6.9 Hz, CH(**Me**)Me); 0.79 (d, 3H, J = 6.9 Hz, CH(Me)**Me**) ^{13}C NMR: (75 MHz, $CDCl_3$) δ 192.9, 172.3, 171.6, 158.3, 155.0, 152.5, 144.2, 137.2, 136.7, 133.2, 131.3, 130.3, 129.4, 129.3, 129.1, 128.7, 128.6, 128.33, 128.29, 128.1, 127.9, 127.6, 124.7, 120.9, 116.5, 112.3, 110.2, 78.1, 77.2, 70.5, 63.7, 52.5, 52.1, 38.1, 33.9, 18.0, 17.91, 17.88, 17.7, 17.6, 17.3, 17.2, 12.3 HRMS: (FAB+) exact mass calculated for

[M+H] ($C_{42}H_{55}N_2O_7Si$) requires *m/z* 727.3779, found *m/z* 727.3758; $[\alpha]_D^{25}$= –60.33 (c = 1.0 $CHCl_3$).



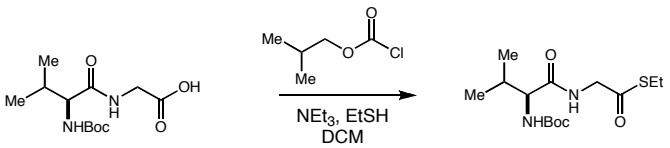
Aldehyde 19: To a solution of amino aldehyde **16a** (354 mg, 0.487 mmol), pyridine (0.1 mL, 1.2175 mmol), and DMAP (29.7 mg, 0.2435 mmol) in 5 mL of dichloromethane at 0 °C was added trifluoroacetic anhydride (0.172 mL, 1.22 mmol) dropwise by syringe under argon. After 30 minutes the reaction was diluted with 50 mL of ethyl acetate and washed with 30 mL of saturated sodium bicarbonate solution. The layers were separated and the organic fraction was washed with brine and dried over sodium sulfate. Purification by flash chromatography on silica gel (25% ethyl acetate in hexanes) gave the title compound product as an amorphous yellow solid in 89% yield (354 mg) in an inseparable 3.5:1 mixture of diastereomers. IR (Film): 3415, 2945, 2867, 1731, 1663, 1610, 1494, 1462, 1203, 1182, 1154, 948, 881, 822, 738 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) 9.67 (d, 1H, J = 7.2 Hz, C**H**O), 7.50–6.75 (m, 13H, Ar**H,** CHOCH=C**H** and CON**H**); 6.57 (d, 1H, J = 1.2 Hz, OC**H**N), 6.21 (dd, 1H, J = 7.5 and 15.9 Hz, C**H**OCH=CH), 5.20 (app q, 2H, OC**H**$_2$PH), 4.92 (m, 1H, CONHC**H**), 4.13 (d, 1H, J = 3.3 Hz, C**H**OTIPS), 3.65 (s, 3H, CO_2**Me**), 3.06 (m, 2H, **CH**$_2$Ar); 2.00–1.85 (m, 1H, C**H**$(CH_3)_2$), 1.10–0.95 (m, 21H, TIPS); 0.89 (d, 3H, J = 7.2 Hz, CH(**Me**)Me), 0.79 (d, 3H, J = 7.2 Hz, CH(Me)**Me**) ^{13}C NMR: (75 MHz, $CDCl_3$) δ 192.2, 172.5, 171.7, 157.5, 151.3, 149.9, 136.5, 135.4, 135.3, 135.1, 131.4, 130.8, 130.7, 129.3, 128.8, 128.5, 128.3,

128.2, 127.3, 124.7, 118.1, 116.7, 114.7, 114.3, 110.7, 100.6, 78.3, 71.0, 63.6, 60.6, 52.8, 52.5, 52.4, 38.3, 34.1, 21.2, 18.2, 18.1, 18.0, 17.7, 17.5, 17.3, 14.4, 12.6, 12.5 HRMS: (FAB+) exact mass calculated for [M+H] ($C_{44}H_{54}N_2O_8F_3Si$) requires *m/z* 823.3601, found *m/z* 823.3560; $[\alpha]_D^{25} = -88.69$ (c = 1.0 $CHCl_3$).



Aldehyde 20: A stream of ozone is passed through a solution of α,β-unsaturated aldehyde **19** (2.52 g, 3.06 mmol) in 40 mL of dichloromethane and 4 mL of methanol at –78 °C for 45 minutes. The solution was bubbled through with oxygen for ten minutes and then quenched by the addition of triphenylphospine (0.96 g, 3.67 mmol). After warming to room temperature overnight, the reaction mixture was concentrated *in vacuo* and loaded directly onto a silica gel column. Elution with 35% ethyl acetate in hexanes gives 2.10 g of title product (87%) as an amorphous white solid in a 3.5:1 mixture of diastereomers. IR (film): 3414, 2945, 2868, 1729, 1666, 1610, 1492, 1462, 1203, 1181, 1158, 986, 881, 822, 738, 681 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) 10.05 (s, 1H, C**H**O), 7.50–6.80 (m, 13H, Ar**H,** OC**H**NTFA and CON**H**), 5.19 (app q, 2H, OC**H**$_2$PH), 4.94 (m, 1H, CONHC**H**), 4.14 (d, 1H, J = 3.3 Hz, C**H**OTIPS), 3.65 (s, 3H, CO_2**Me**), 3.07 (m, 2H, **CH**$_2$Ar), 2.0–1.85 (m, 1H, C**H**$(CH_3)_2$), 1.10–0.95 (m, 21H, TIPS), 0.88 (d, 3H, J = 7.2 Hz, CH(**Me**)Me), 0.79 (d, 3H, J = 6.6 Hz, CH(Me)**Me**) ^{13}C NMR: (75 MHz, $CDCl_3$) δ 191.7, 173.0, 172.7, 171.8, 171.7, 157.0, 149.8, 136.9, 136.5, 135.0, 132.4, 131.7, 131.0,

130.9, 130.5, 129.6, 129.5, 129.2, 128.8, 128.7, 128.2, 128.0, 127.3, 125.2, 124.2, 118.0, 116.0, 115.3, 114.2, 110.9, 109.8, 99.1, 96.1, 78.3, 71.1, 70.8, 60.7, 56.1, 52.7, 52.4, 38.7, 38.2, 34.1, 33.9, 33.8, 21.3, 18.2, 18.1, 17.8, 17.7, 17.5, 17.4, 17.2, 14.4, 12.55, 12.51 HRMS: (FAB+) exact mass calculated for [M+H] ($C_{42}H_{52}N_2O_8F_3Si$) requires *m/z* 797.3445, found *m/z* 797.3420; $[\alpha]_D^{25} = -112.22$ (c = 1.0 $CHCl_3$).



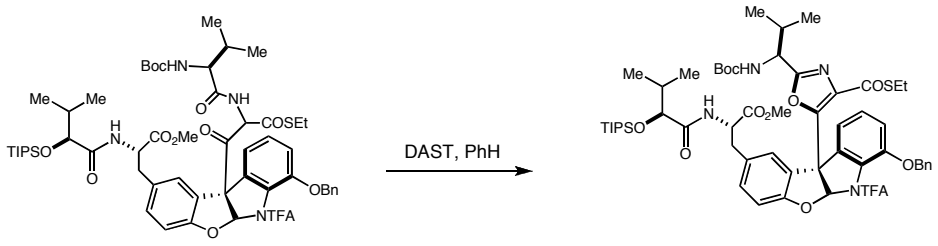
21

Thioester 21: To a 0 °C solution of commercially available *N*-Boc-valinylglycine (2.96 g, 10.79 mmol) in 50 mL of CH_2Cl_2 under argon was added NEt_3 (3.91 mL, 28.054 mmol) followed by isobutyl chloroformate (1.66 mL, 12.95 mL). After 1 hour at 0 °C was added ethanethiol (1.67 mL, 2.0 mmol) and the reaction was warmed to room temperature and stirred for ten hours. The reaction mixture was then diluted with $NaHCO_3$ and extracted 3 x 100 mL of CH_2Cl_2. The combined organic layer was washed with 200 mL of brine and concentrated. The resulting oil was recrystallized from a hot solution of 10% ethyl acetate in hexanes to give the title compound as a white crystalline solid in 85% yield (2.90 g). IR (Thin Film): 3310, 3077, 2968, 2932, 1688, 1663, 1525, 1392, 1366, 1298, 1247, 1170, 1094, 1043, 1016, 966 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ 6.66 (br s, 1H, N**H**), 5.03 (br s, 1H, N**H**Boc), 4.19 (d, 2H, J = 5.4 Hz, NHC**H$_2$**), 4.00 (dd, 1H, J = 6.0, 8.4 Hz, C**H**NHBoc), 2.91 (q, 2H, J = 7.5 Hz, SC**H$_2$**), 2.21 (m, 1H, C**H**Me(Me)), 1.44 (s, 9H, O**tBu**), 1.25 (t, 3H, J = 7.5 Hz, SCH_2**CH_3**), 0.98 (d, 3H, J = 6.9

Hz, CH**Me**(Me)), 0.94 (d, 3H, J = 6.9 Hz, CHMe(**Me**)); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 196.9, 172.2, 156.2, 80.3, 60.1, 49.2, 30.9, 28.5, 23.4, 19.6, 17.9, 14.8; HRMS: (FAB+) exact mass calculated for [M+H] ($C_{14}H_{27}N_2O_4S$) requires *m/z* 319.1702, found *m/z* 319.1692; $[\alpha]_D^{25} = -17.01$ (c = 1.0 $CHCl_3$).

Ketoamide 23: To a solution of thioester **21** (461 mg, 1.449 mmol) in 6.0 mL of CH_2Cl_2 at –78 °C under an argon balloon was added $TiCl_4$ (0.334 mL, 3.029 mmol) and the resulting solution turned bright yellow. After 30 minutes triethylamine (0.423 mL, 3.029 mmol) was added turning the reaction mixture dark purple. After 30 minutes more MeCN (0.1375 mL, 2.634 mmol) was added. Ten minutes after aldehyde **20** (1.05 g, 1.317 mmol) was added dropwise as a solution in 1.5 mL of CH_2Cl_2. The dark purple reaction mixture was stirred at –78 °C for 1 hour then placed in a –30 °C refrigerator for 12 hours. At this time the reaction was diluted with CH_2Cl_2 and quenched with a saturated solution of $NaHCO_3$. The layers were separated and the organic layer was washed with 2 x 50 mL of water then 50 mL of brine. The organic fractions were concentrated and purified by column chromatography (20%–25% ethyl acetate in hexanes) to afford the title compound as an amorphous yellow solid. This solid was immediately dissolved in 17.5 mL of CH_2Cl_2 and Dess-Martin periodinane (1.11 g, 2.62 mmol) was added. After two

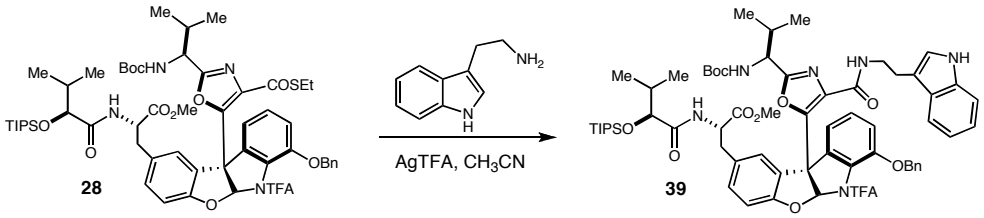
hours the solution was diluted with ethyl acetate and washed with a saturated solution of $NaHCO_3$. The organic fractions were concentrated and the resulting oil purified by column chromatography to afford in 65% yield over the two steps the title compound (1.05 g) as an off-yellow solid as a 3.5:3.5:1:1 mixture of inseparable diastereomers by ^1H NMR. This material was carried on without further purification. HRMS: (FAB+) exact mass calculated for [M+H] ($C_{56}H_{76}N_4O_{12}F_3SiS$) requires *m/z* 113.490, found *m/z* 113.491; $[\alpha]_D^{25} = -31.69$ (c = 1.0 $CHCl_3$) (for ketoamide).



23 **28**

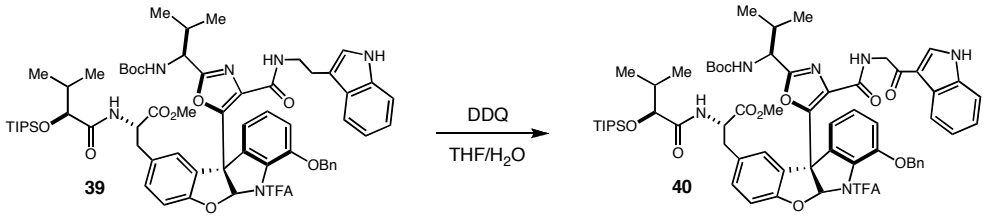
Oxazole 28: To a solution of **23** (900 mg, 0.8 mmol) in benzene (15 mL) was added DAST (1.5 mL) dropwise by syringe. The solution was stirred at room temperature for one hour before being diluted with a saturated solution of $NaHCO_3$. The layers were separated and the organic was washed with ethyl acetate 3 x 50 mL. The combined organics were washed with brine and concentrated. The resulting oil was purified on silica gel (20%–25% ethyl acetate in hexanes) to yield the title compound (500 mg, 55%) as pale yellow solid. IR (film): 3415, 2963, 2868, 2360, 2340, 1732, 1674, 1608, 1495, 1464, 1367, 1290, 1253, 1203, 1159, 1125, 1001, 878, 822, 738, 685, 668 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$): 7.80–6.80 (m, 13H, Ar-**H,** OC**H**NTFA and CON**H**), 5.59 (br d, 1H, J = 9.3 Hz, N**H**Boc), 5.17 (app q, 2H, OC$\mathbf{H}_2$Ph), 4.94 (m, 1H, CONHC**H**), 4.90 (m, 1H,

C**H**NHBOC), 4.08 (d, 1H, J = 3.6 Hz, C**H**OTIPS), 3.59 (S, 3H, CO_2**Me**), 3.00 (M, 2H, C**H**$_2$Ar), 2.76 (q, 2H, J = 7.5 Hz, C**H**$_2$$CH_3$), 2.19 (m, 1H, NHCHC**H**$(CH_3)_2$), 1.85 (m, 1H, OCHC**H**$(CH_3)_2$), 1.47 (br s, 9H, Boc), 1.20 (t, 3H, J = 7.5 Hz, CH_2C**H**$_3$), 0.99 (m, 27H, TIPS and NHCHCH(**CH**$_3$)$_2$), 0.79 (d, 3H, J = 7.2 Hz, OCHCH(**Me**)Me); 0.75 (d, 3H, J = 6.9 Hz, CH(Me)**Me**); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 186.8, 183.4, 180.6, 174.2, 172.2, 171.6, 163.5, 162.7, 161.8, 157.5, 155.6, 154.2, 153.7, 149.8, 149.4, 137.0, 136.4, 135.5, 135.0, 134.0, 133.1, 132.4, 131.0, 129.7, 128.5, 127.9, 127.7, 127.1, 125.1, 116.2, 115.5, 114.2, 110.1, 99.7, 94.6, 80.0, 78.1, 70.8, 60.1, 59.1, 54.4, 52.1, 47.9, 38.4, 33.7, 32.5, 28.3, 28.0, 22.9, 18.8, 18.2, 17.9, 17.8, 17.4, 17.1, 16.7, 16.0, 14.2, 13.6, 12.3; ^{19}F NMR: (75 MHz, $CDCl_3$) δ –70.4 (s, 3F, CF_3); HRMS: (FAB+) exact mass calculated for [M–H] ($C_{56}H_{72}N_4O_{11}F_3SiS$) requires *m/z* 1093.464, found *m/z* 1093.464; $[\alpha]_D^{25}$ = –44.62 (c = 1.0 $CHCl_3$).



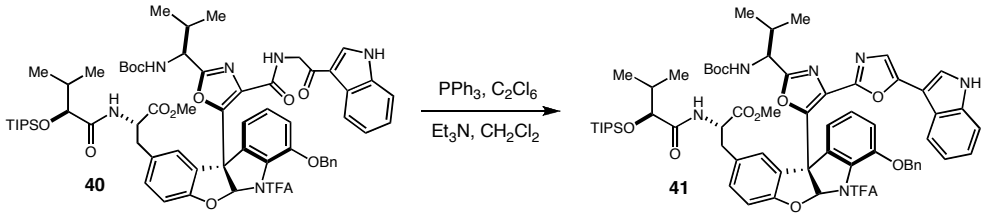
Amide 39: To **28** (100 mg, 0.091 mmol), tryptamine (51 mg, 0.318 mmol) and AgTFA (46 mg, 0.209 mmol) in a light-protected round-bottom flask was added degassed CH_3CN (1.8 mL) with stirring. The solution was warmed to 40 °C and held for 45 minutes before being diluted with Et_2O and passed through celite. After concentration, the resulting oil was purified on silica gel (40%–80% Et_2O in hexanes) to yield the title compound (87 mg, 87%) as pale yellow solid. IR (film): 3410, 2961, 2868, 1724, 1672, 1607, 1494,

1458, 1367, 1288, 1204, 1159, 1011, 880, 821, 739, 684 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$): 8.14 (s, 1H, C=CN**H**), 7.78 (d, 1H, Ar-**H**, 1.2 Hz), 7.58–6.76 (m, 17H, Ar-**H,** OC**H**NTFA and CON**H**), 5.49 (br d, 1H, J = 9.3 Hz, N**H**Boc), 5.16 (m, 2H, OC**H**$_2$Ph), 4.95 (m, 1H, CONHC**H**), 4.75 (m, 1H, C**H**NHBOC), 4.09 (d, 1H, J = 3.6 Hz, C**H**OTIPS), 3.58 (m, 5H, CO_2**Me**, NHC**H**$_2$CH$_2$), 3.00 (m, 4H, C**H**$_2$Ar, NHC**H**$_2$C**H**$_2$), 2.14 (m, 1H, NHCHC**H**$(CH_3)_2$), 1.88 (m, 1H, OCHC**H**$(CH_3)_2$), 1.44 (br s, 9H, Boc), 0.99 (m, 27H, TIPS and NHCHCH(**CH**$_3$)$_2$), 0.78 (d, 3H, J = 7.2 Hz, OCHCH(**Me**)Me); 0.72 (d, 3H, J = 7.2 Hz, CH(Me)**Me**); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 172.3, 171.7, 162.0, 160.0, 157.5, 155.5, 150.0, 149.4, 136.5, 136.3, 135.6, 130.8, 130.3, 129.4, 128.5, 128.4, 128.3, 127.8, 127.4, 127.3, 127.0, 126.9, 124.8, 122.1, 122.0, 119.3, 118.6, 116.5, 114.0, 112.8, 111.2, 110.0, 100.1, 80.1, 78.1, 70.7, 60.0, 54.4, 52.2, 52.1, 39.3, 38.4, 33.9, 33.7, 32.3, 28.4, 25.2, 18.8, 18.2, 18.0, 17.9, 17.8, 17.4, 17.1, 12.3; ^{19}F NMR: (75 MHz, $CDCl_3$) δ -70.4 (s, 3F, CF_3); HRMS: (FAB+) exact mass calculated for [M+H] ($C_{64}H_{78}N_6O_{11}F_3Si$) requires *m/z* 1192.551, found *m/z* 1192.547; $[\alpha]_D^{25} = -45.64$ (c = 1.0 $CHCl_3$).



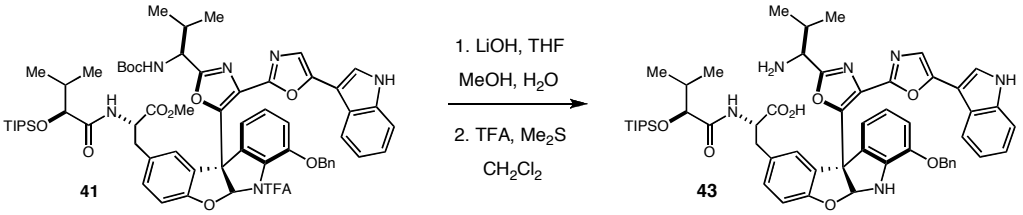
Ketoindole 40: To a solution of **39** (300 mg, 0.25 mmol) in THF/H_2O (10:1, 5 mL) was added DDQ (122 mg, 0.75 mmol). The solution was stirred at room temperature for 15 minutes before being diluted with a saturated solution of $NaHCO_3$. The layers were separated and the aqueous was washed with ethyl acetate 3 x 50 mL. The combined

organics were washed with brine and concentrated. The resulting oil was purified on silica gel (60%–80% Et_2O in hexanes) to yield the title compound (228 mg, 75%) as pale yellow solid. IR (Film): 3406, 2962, 2868, 1732, 1674, 1608, 1511, 1495, 1455, 1367, 1288, 1247, 1204, 1159, 1126, 1009, 910, 881, 822, 736, 685, 648 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$): 9.63 (d, 1H, C=CN**H**, 2.1 Hz), 8.21 (d, 1H, Ar-**H**, 6.9 Hz), 7.98 (t, 1H, Ar-**H**, 4.8 Hz), 7.61–6.75 (m, 16H, Ar-**H,** OC**H**NTFA and CON**H**), 5.62 (br d, 1H, J = 9.0 Hz, N**H**Boc), 5.09 (m, 2H, OC**H**$_2$Ph), 4.95 (m, 1H, CONHC**H**), 4.80 (m, 1H, C**H**NHBOC), 4.45 (t, 2H, J = 5.0 Hz, C**H**$_2$CO), 4.09 (d, 1H, J = 3.6 Hz, C**H**OTIPS), 3.59 (s, 3H, CO_2**Me**), 3.03 (m, 2H, C**H**$_2$Ar), 2.20 (m, 1H, NHCHC**H**$(CH_3)_2$), 1.87 (m, 1H, OCHC**H**$(CH_3)_2$), 1.47 (br s, 9H, Boc), 0.99 (m, 27H, TIPS and NHCHCH(**CH**$_3$)$_2$), 0.77 (d, 3H, J = 7.2 Hz, OCHCH(**Me**)Me); 0.71 (d, 3H, J = 7.2 Hz, CH(Me)**Me**); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 186.5, 172.3, 171.6, 162.4, 160.2, 157.5, 155.6, 155.5, 151.1, 149.3, 136.4, 136.3, 135.8, 132.0, 130.8, 130.3, 129.5, 128.7, 128.5, 128.2, 127.8, 127.0, 125.5, 125.3, 125.2, 123.7, 122.7, 121.8, 118.1, 116.2, 114.7, 114.3, 114.0, 111.9, 110.0, 100.3, 80.2, 78.2, 70.7, 65.9, 60.1, 54.5, 52.5, 52.1, 45.7, 38.3, 34.2, 33.8, 33.7, 32.6, 30.3, 28.4, 18.8, 18.2, 18.0, 17.9, 17.8, 17.4, 17.1, 15.3, 12.3; ^{19}F NMR: (75 MHz, $CDCl_3$) δ –70.2 (s, 3F, CF_3); HRMS: (FAB+) exact mass calculated for [M–H] ($C_{64}H_{78}N_6O_{12}F_3Si$) requires *m/z* 1207.540, found *m/z* 1207.536; $[\alpha]_D^{25}$ = –40.21 (c = 1.0 $CHCl_3$).



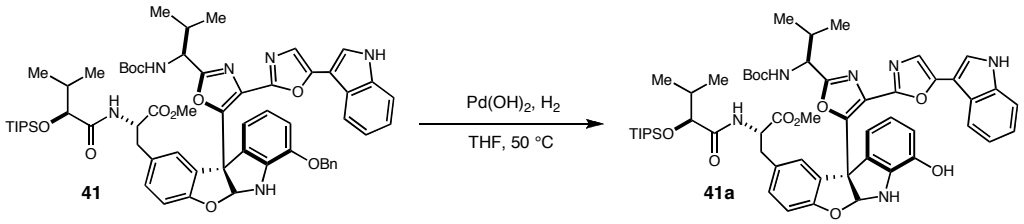
Bisoxazole 41: To a solution of PPh_3 (186 mg, 0.71 mmol) in CH_2Cl_2 (6.6 mL) was added C_2Cl_6 (168 mg, 0.71 mmol). The solution was stirred at room temperature for 10 minutes at which time Et_3N (0.20 mL, 1.42 mmol) was added dropwise. The resultant solution was stirred for 10 minutes at which time it was added dropwise via cannula to a stirred CH_2Cl_2 (2.8 mL) solution of **40** (171 mg, 0.142 mmol) held at -15 °C. After addition was complete, the reaction was warmed to 0 °C and held at this temperature for 10 minutes, at which point it was allowed to warm to room temperature and stirred for an additional 10 minutes. The solution was then diluted with a saturated solution of $NaHCO_3$. The layers were separated and the aqueous was washed with CH_2Cl_2 (3 x 20 mL). The combined organics were washed with brine and concentrated. The resulting oil was purified on silica gel (50%–70% Et_2O in hexanes) to yield the title compound (157 mg, 93%) as a pale off-white solid. IR (film): 3406, 2962, 2868, 1733, 1674, 1610, 1495, 1458, 1367, 1288, 1256, 1203, 1156, 1124, 1057, 997, 882, 741, 668 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$): 8.58 (s, 1H, C=CN**H**), 7.74–6.76 (m, 19H, Ar-**H,** OC**H**NTFA and CON**H**), 5.71 (br d, 1H, J = 9.0 Hz, N**H**Boc), 5.11 (app d, 2H, OC**H**$_2$Ph, J = 3.6 Hz), 4.92 (m, 1H, CONHC**H**), 4.82 (m, 1H, C**H**NHBOC), 4.09 (d, 1H, J = 3.3 Hz, C**H**OTIPS), 3.57 (s, 3H, CO_2**Me**), 2.98 (m, 2H, C**H**$_2$Ar), 2.20 (m, 1H, NHCHC**H**$(CH_3)_2$), 1.86 (m, 1H, OCHC**H**$(CH_3)_2$), 1.46 (br s, 9H, Boc), 0.99 (m, 27H, TIPS and NHCHCH(**CH**$_3$)$_2$), 0.77 (d, 3H, J = 6.9 Hz, OCHCH(**Me**)Me); 0.69 (d, 3H, J = 6.9 Hz, CH(Me)**Me**); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 172.5, 171.8, 164.1, 163.3, 161.6, 161.5, 161.4, 161.3, 161.2, 157.6, 156.0, 155.8, 155.6, 151.7, 150.8, 149.4, 148.7, 147.5, 136.7, 136.4, 131.2, 130.2, 128.9, 128.8, 128.2, 128.1, 127.4, 125.8, 125.7, 124.0, 123.2, 123.1, 121.5, 121.1, 119.9, 118.3, 116.2, 114.3, 111.9, 110.4, 104.9, 100.3, 80.2, 78.4, 70.9, 60.6, 54.8, 52.5, 52.3, 38.6,

33.9, 33.1, 30.6, 28.6, 19.0, 18.5, 18.2, 18.1, 18.0, 17.7, 17.3, 12.5; ^{19}F NMR: (75 MHz, $CDCl_3$) δ –70.3 (s, 3F, CF_3); HRMS: (FAB+) exact mass calculated for [M–H] ($C_{64}H_{76}N_6O_{11}F_3Si$) requires *m/z* 1189.529, found *m/z* 1189.525; $[\alpha]_D^{25}$ = –21.03 (c = 1.0 $CHCl_3$).



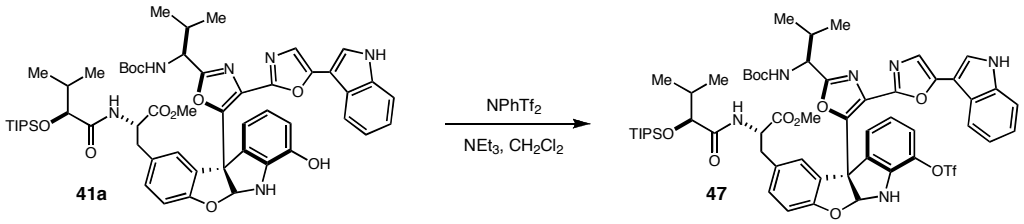
Amino Acid 43: To a solution of **41** (157 mg, 0.132 mmol) in THF/MeOH/H_2O (10:2:1, 4.4 mL) was added LiOH•H_2O (56 mg, 1.32 mmol). The solution was stirred at room temperature for 1 hour at which time it was acidified with 1% aqueous HCl to pH 2. The aqueous layer was extracted 3x with EtOAc, the organics combined and dried over Na_2SO_4. Following concentration, the resultant carboxylic acid was redissolved in CH_2Cl_2 (2.4 mL). To this solution was then added Me_2S (0.6 mL) and trifluoroacetic acid (1.2 mL) with stirring. After stirring for 25 minutes, the solvents were removed *in vacuo*, and the resulting solid redissolved in benzene and concentrated three successive times in order to remove residual trifluoroacetic acid. The resulting solid was purified on silica gel (5%–10% MeOH in CH_2Cl_2) to yield the title compound (125 mg, 88%) as a yellow solid. IR (film): 3397, 2958, 2929, 2862, 1676, 1622, 1497, 1458, 1387, 1204, 1138, 1054, 996, 881, 801, 727 cm^{-1}; ^{1}H NMR: (300 MHz, CD_3OD): 7.70–6.52 (m, 19H, Ar-**H,** OC**H**NH and CON**H**), 4.82 (app d, 2H, OC**H**$_2$Ph, J = 11.7 Hz), 4.37 (d, 1H, CONHC**H**, J = 5.1 Hz), 4.29 (d, 1H, C**H**NH_2, J = 7.5 Hz), 4.01 (d, 1H, J = 4.2 Hz, C**H**OTIPS), 2.93

(m, 2H, C**H**$_2$Ar), 2.30 (m, 1H, NHCHC**H**$(CH_3)_2$), 1.78 (m, 1H, OCHC**H**$(CH_3)_2$), 1.04 (m, 27H, TIPS and NHCHCH(**C**$\mathbf{H}_3)_2$), 0.74 (d, 3H, J = 6.9 Hz, OCHCH(**Me**)Me); 0.68 (d, 3H, J = 6.9 Hz, CH(Me)**Me**); ^{13}C NMR: (75 MHz, CD_3OD) δ 173.2, 172.6, 158.8, 158.6, 152.6, 151.5, 149.9, 143.9, 138.2, 137.7, 136.7, 132.4, 132.3, 131.7, 131.6, 130.0, 129.2, 129.0, 128.8, 128.7, 128.5, 128.2, 128.0, 127.5, 127.4, 127.1, 127.0, 126.9, 126.2, 124.6, 123.7, 122.1, 120.2, 120.1, 119.3, 118.9, 118.5, 114.6, 112.2, 11.6, 109.5, 103.6, 103.2, 78.2, 69.6, 67.4, 60.3, 53.9, 53.7, 52.3, 37.0, 33.5, 31.2, 29.5, 25.1, 23.3, 18.9, 17.5, 17.1, 17.0, 16.9, 16.6, 16.5, 16.3, 12.1; HRMS: (FAB+) exact mass calculated for [M+H] ($C_{56}H_{67}N_6O_8Si$) requires *m/z* 979.4790, found *m/z* 979.4801; $[\alpha]_D^{25}$ = –42.16 (c = 1.0 MeOH).



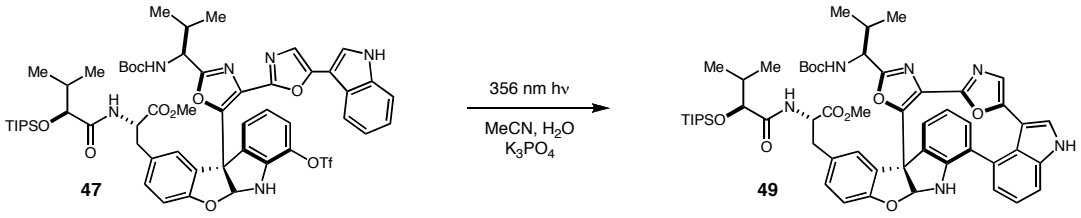
Phenol 41a: To a solution of **41** (192 mg, 0.161 mmol) in THF (10 mL) was added $Pd(OH)_2$/C (80 mg). The solution was sparged with H_2 for 20 minutes and warmed to 50 °C under H_2 with stirring. After 18 hours, the solution was then filtered through celite. After concentration, the resulting oil was purified on silica gel (70%–90% Et_2O in hexanes) to yield the title compound (144 mg, 89%) as a pale off-white solid. IR (film): 3327, 2962, 2868, 1748, 1671, 1633, 1611, 1500, 1463, 1367, 1292, 1250, 1172, 1058, 1014, 917, 881, 820, 736, 684 cm^{-1}; ^{1}H NMR: (300 MHz, $CDCl_3$): 9.24 (s, 1H, C=CN**H**), 7.60–6.52 (m, 14H, Ar-**H,** OC**H**NH and CON**H**), 5.74 (br d, 1H, J = 9.0 Hz, N**H**Boc),

4.85 (m, 2H, CONHC**H**, C**H**NHBOC), 4.09 (d, 1H, J = 3.3 Hz, C**H**OTIPS), 3.50 (s, 3H, CO_2**Me**), 2.93 (m, 2H, C$\mathbf{H_2}$Ar), 2.16 (m, 1H, NHCHC**H**$(CH_3)_2$), 1.83 (m, 1H, OCHC**H**$(CH_3)_2$), 1.39 (br s, 9H, Boc), 0.98 (m, 27H, TIPS and NHCHCH(**CH$_3$**)$_2$), 0.73 (d, 3H, J = 7.2 Hz, OCHCH(**Me**)Me); 0.67 (d, 3H, J = 7.2 Hz, CH(Me)**Me**); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 172.7, 171.6, 163.2, 158.1, 156.0, 152.0, 148.8, 141.7, 136.5, 136.2, 130.4, 130.0, 129.4, 129.2, 128.9, 125.8, 125.2, 123.8, 123.7, 123.5, 122.6, 121.2, 120.6, 119.3, 116.0, 115.7, 111.8, 110.0, 104.3, 104.2, 103.3, 80.2, 78.2, 60.6, 54.6, 52.6, 52.1, 52.0, 38.4, 33.8, 32.6, 31.6, 29.7, 28.3, 18.9, 18.3, 18.1, 17.9, 17.5, 17.4, 12.3; HRMS: (FAB+) exact mass calculated for [M+H] ($C_{55}H_{71}N_6O_{10}Si$) requires *m/z* 1003.500, found *m/z* 1003.503; $[\alpha]_D^{25} = -12.89$ (c = 0.073 $CHCl_3$).



Triflate 47: To a solution of **41a** (45 mg, 0.045 mmol) in CH_2Cl_2 (0.9 mL) was added $PhNTf_2$ (20 mg, 0.056 mmol) and Et_3N (19 μL, 0.134 mmol). The solution was stirred under argon for 30 minutes and then diluted with saturated $NaHCO_3$. The aqueous layer was washed with EtOAc, and the combined organics were washed with H_2O and dried over Na_2SO_4. After concentration of the solvents *in vacuo*, the resulting oil was purified on silica gel (20% EtOAc in hexanes) to yield the title compound (44 mg, 86%) as a pale off-white solid. IR (film): 3307, 2963, 2868, 1672, 1630, 1497, 1424, 1367, 1211, 1140, 1058, 998, 908, 881, 815, 740, 684 cm^{-1}; ^{1}H NMR: (300 MHz, $CDCl_3$): 8.55 (d, 1H,

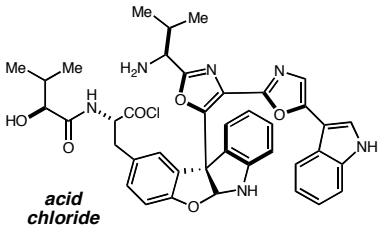
C=CN**H**, J = 1.8 Hz), 7.75–6.70 (m, 14H, Ar-**H,** OC**H**NH and CON**H**), 5.68 (br d, 1H, J = 9.0 Hz, N**H**Boc), 4.90, (m, 1H, CONHC**H),** 4.78 (m, 1H, C**H**NHBOC), 4.06 (d, 1H, J = 3.6 Hz, C**H**OTIPS), 3.52 (s, 3H, CO_2**Me**), 2.95 (m, 2H, C$\mathbf{H_2}$Ar), 2.16 (m, 1H, NHCHC**H**$(CH_3)_2$), 1.83 (m, 1H, OCHC**H**$(CH_3)_2$), 1.45 (br s, 9H, Boc), 0.98 (m, 27H, TIPS and NHCHCH(**C**$\mathbf{H_3}$)$_2$), 0.74 (d, 3H, J = 6.9 Hz, OCHCH(**Me**)Me); 0.67 (d, 3H, J = 6.9 Hz, CH(Me)**Me**); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 172.6, 171.8, 163.6, 158.4, 155.9, 152.0, 149.4, 148.6, 141.3, 136.5, 133.5, 130.9, 130.0, 129.5, 128.0, 126.6, 125.6, 124.1, 123.1, 121.8, 121.6, 121.1, 121.0, 119.8, 116.7, 112.0, 110.7, 104.9, 103.1, 80.2, 78.4, 60.3, 54.8, 52.6, 52.3, 38.6, 33.9, 33.0, 31.8, 29.9, 28.6, 18.9, 18.6, 18.2, 18.1, 17.9, 12.5; ^{19}F NMR: (75 MHz, $CDCl_3$) δ –73.5 (s, 3F, CF_3); HRMS: (FAB+) exact mass calculated for [M+H] ($C_{56}H_{70}N_6O_{12}F_3SiS$) requires *m/z* 1135.449, found *m/z* 1135.449; $[\alpha]_D^{25}$ = –10.74 (c = 0.94 $CHCl_3$).



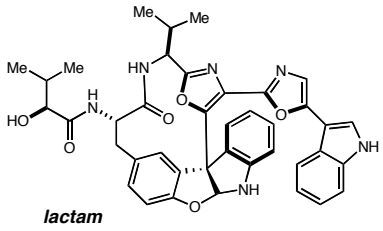
Biaryl 49: Triflate **47** (5 mg, 0.0044 mmol) and K_3PO_4 (0.95 mg, 0.0044 mmol) were dissolved in degassed CH_3CN/H_2O (3:1, 2ml) in a Pyrex flask under argon. This solution was exposed to 356 nm UV light (Hitachi UVA lamps, Luzchem 10 lamp photoreactor) with stirring for 1 hour. At this time the solvents were concentrated *in vacuo*, and the resulting oil was purified on silica gel (50% EtOAc in hexanes) to yield the title compound (1.9 mg, 38%) as a pale off-white solid. IR (film): 3312, 2961, 2927, 2868,

1715, 1673, 1592, 1493, 1456, 1367, 1259, 1210, 1172, 1095, 1016, 914, 882, 803, 739, 685 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$): 8.71 (s, 1H, C=CN**H**), 7.71–6.75 (m, 12H, Ar-**H,** CON**H**), 6.32 (s, 1H, OC**H**NH), 5.71 (br d, 1H, J = 9.6 Hz, N**H**Boc), 5.03, (m, 1H, CONHC**H)**, 4.78 (m, 1H, C**H**NHBOC), 4.11 (d, 1H, J = 3.6 Hz, C**H**OTIPS), 3.71 (s, 3H, CO_2**Me**), 3.15 (m, 2H, C$\mathbf{H_2}$Ar), 2.14 (m, 1H, NHCHC**H**$(CH_3)_2$), 1.81 (m, 1H, OCHC**H**$(CH_3)_2$), 1.48 (br s, 9H, Boc), 1.06–0.77 (m, 33H, TIPS, NHCHCH(**C**$\mathbf{H_3}$)$_2$, and OCHCH(**Me**)**Me**); HRMS: (FAB+) exact mass calculated for [M+H] ($C_{55}H_{69}N_6O_9Si$) requires *m/z* 985.4895, found *m/z* 985.4897; $[\alpha]_D^{25} = -28.03$ (c = 0.1, $CHCl_3$).

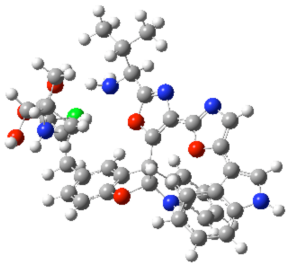
DFT calculations regarding lactamization thermochemistry: Calculations were carried out at using the B3LYP functional at the 3-21G level of theory in the Gaussian 03 suite of programs. Minimized structures are shown below with their respective energies.

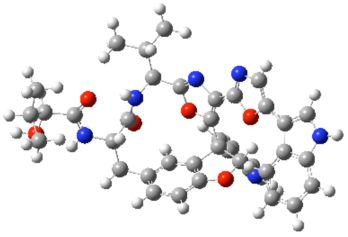


acid chloride



lactam





	hartrees	ΔE (hartree)	ΔE (kcal)
acyl chloride	-2772.826609		
lactam	-2314.248821		
HCl	-458.5887638		
		-0.01097533	-6.887123841

Coordinates, Level of Calculation, and Energies for DFT Structures:

Acyl Chloride
E (B3LYP/3-21G) = –2772.82660927 a.u.

0 1

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C	2.09625700	-3.62551400	-0.33901800
C	0.84280000	-3.58197300	-0.96128500
C	-0.04971800	-2.58756900	-0.57370700
O	-1.27860400	-2.35114100	-1.16503200
C	-0.41320000	0.72152700	0.48486800
C	-1.60094300	-0.92608500	1.97565000
C	-0.99194000	1.95772200	0.35577300

N	0.00434200	2.95941100	0.45640300
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C	3.85844700	-2.60972400	1.19888800
C	4.52299200	-1.31829100	0.61612300
O	7.01935900	-1.29770400	0.67024400
C	-2.85749100	-1.50004700	1.71529600
C	2.51809200	2.90180400	0.89819100
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C	4.71202100	-0.31690400	-1.62765700
C	4.53300500	-0.63352200	-3.11575700
C	3.25561000	0.05977200	-3.66122000
C	3.46154500	1.58180600	-3.78967800
C	2.02679500	-0.29319600	-2.79698400
O	4.92901200	0.84510100	-1.21255700
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H	-4.68526000	-2.25891800	2.58126700
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Lactam

E (B3LYP/3-21G) = –2314.24882081 a.u.

0,1

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H	-1.38826900	-0.30356200	4.94014200
H	-2.87891900	0.64939400	5.19427600
H	-7.64791600	-1.04905600	0.06495900
H	-8.54588100	-2.41312900	-1.84732100
H	-7.45250600	-4.58602400	-1.11486200
H	-6.24060100	-3.60835500	-0.23065300
H	-7.94901400	-3.55887800	0.24699300
H	-5.60381000	-2.79048500	-2.63847700
H	-7.02270400	-3.46517300	-3.46725700
H	-6.74124600	-1.70328300	-3.47735900
H	-0.15678000	3.68863600	1.51905400
H	0.53024400	6.08747700	1.73173900
H	2.64700300	6.85837800	0.70213200
H	-3.12391200	-0.58214300	-1.31334200
H	3.35095000	0.55241200	-0.01906600
H	8.38950300	-3.42120100	0.41702900
H	3.90377400	-3.61387900	3.14538900
H	6.67712400	-3.34737800	2.27797200
H	3.87151800	-1.11890200	-1.48622900
H	4.92563100	-0.79622600	-3.67634000
H	7.25599700	-1.53159200	-4.10149000
H	8.58598200	-2.61805800	-2.31136100
H	4.10872100	5.28108900	-0.52927600
O	-7.52962900	0.01378000	-1.77685500
H	-8.49951000	-0.05772600	-1.97158800
C	-3.33000800	0.93467600	0.22111300
N	-3.05997200	-0.04111000	1.12953400
H	-3.33020500	-0.99888900	0.89235300

HCl

E (B3LYP/3-21G) = –458.58876379 a.u.

0 1

Cl	0.00000000	0.00000000	0.07166700
H	0.00000000	0.00000000	-1.21833300

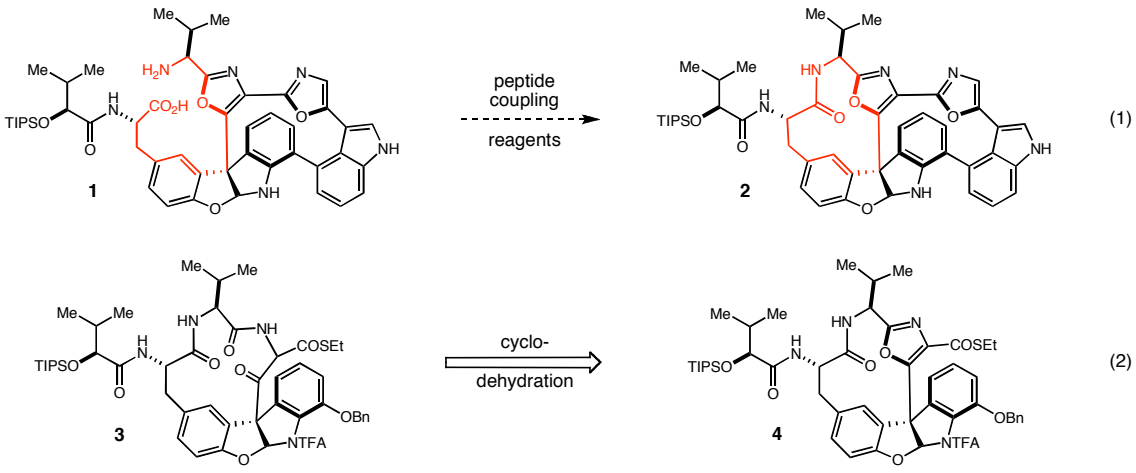
Chapter 4

Second-Generation MacMillan Synthesis of Diazonamide A: Development of a Novel Magnesium-Mediated Macroaldolization

I. Outline of a New Synthetic Strategy

In light of our inability to close the left-hand macrocycle of diazonamide A by a late stage lactamization in our original synthetic route, we were compelled to devise an alternative approach (eq 1). Our foremost concern in doing so was that the strain in this particular 12-membered ring would likely preclude the success of any type of ring closure if all other structural elements of the ring were already in place. This logic suggests first creating a larger and more conformationally flexible ring and subsequently contracting it to the desired size in a second, more energetically favorable synthetic operation. We recognized that this reasoning could be applied to the cyclodehydration of the central A-ring oxazole, prompting us to fully evaluate the risks and benefits of attempting to carry out this ring contraction strategy (eq 2).

Figure 1: Comparison of first- and second-generation strategies toward the left-hand macrocycle

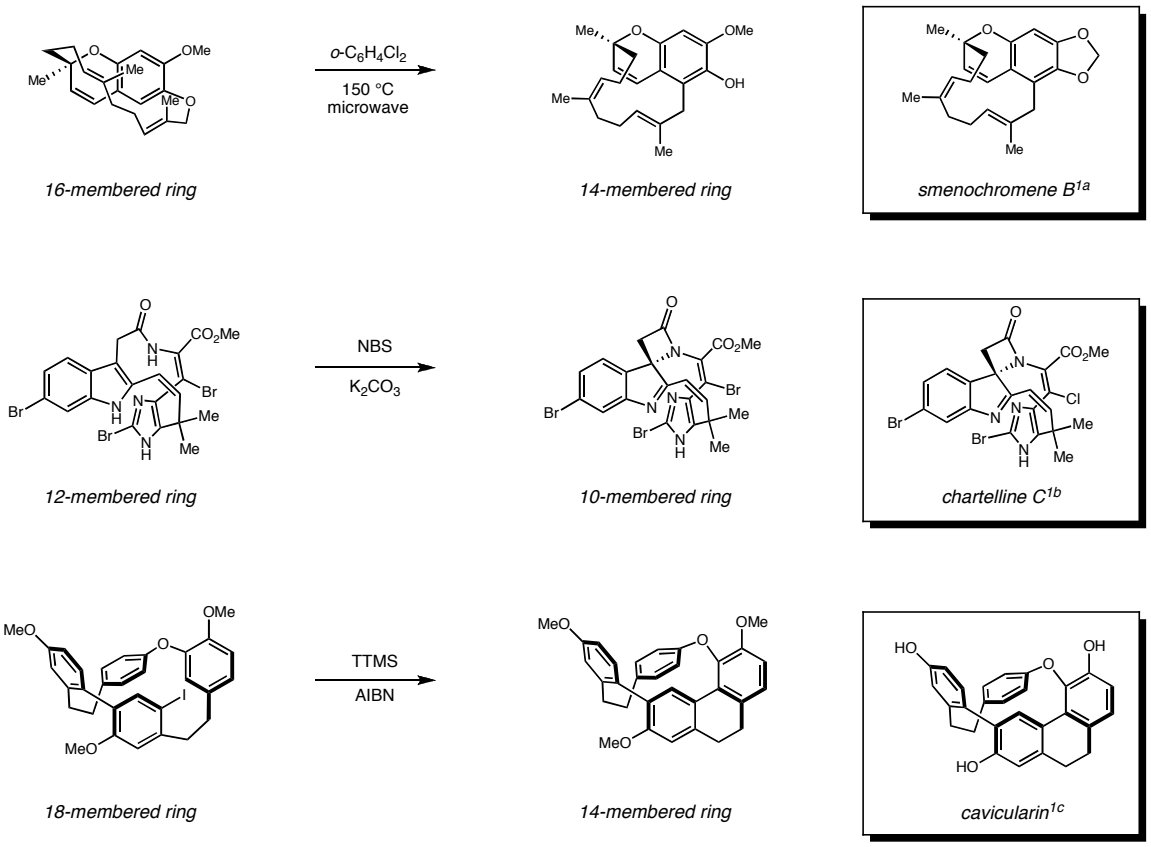


(1)

(2)

In regards to precedence, ring contraction is a classical strategy for the creation of strained cyclic systems and thus we were encouraged by the many previous applications of this idea to the synthesis of large, strained rings.[1] In fact, this concept is still a mainstay in contemporary approaches to macrocyclic targets (Figure 2).

Figure 2: Selected recent examples of ring contraction approaches in natural product synthesis

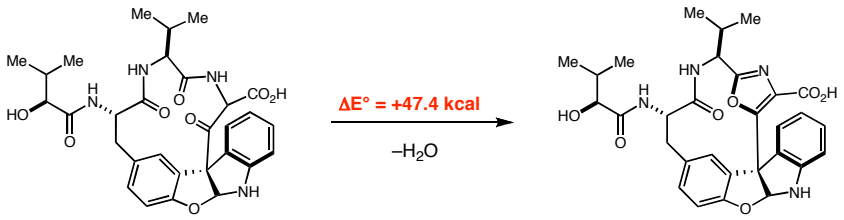


In regards to practicality, the application of this strategy to diazonamide A was seemingly straightforward. Ketoamide **3** would first be synthesized from an appropriate acyclic precursor wherein the A-ring oxazole has yet to be cyclized (Figure 1). We postulated that this 13-membered ring would be considerably more flexible and exhibit

[1] For three recent examples of ring contraction in the synthesis of strained ring systems, see: (a) Rosa, C. P.; Kienzler, M. A.; Olson, B. S.; Liang, G.; Trauner, D. *Tetrahedron* **2007**, *63*, 6529–6534. (b) Baran, P. S.; Shenvi, R. A. *J. Am. Chem. Soc.* **2006**, *128*, 14028–14029. (c) Harrowven, D. C.; Woodcock, T.; Howes, P. D. *Angew. Chem. Int. Ed.* **2005**, *44*, 3899–3901.

substantially less ring strain than its ring-contracted analog in the natural product, and consequently be more favorable to form. DFT calculations validated this reasoning, showing that a simplified ketoamide is 47.4 kcal/mol less strained than its dehydrated oxazole form (Table 1).[2] Once installed, **3** will be cyclodehydrated to yield the A-ring

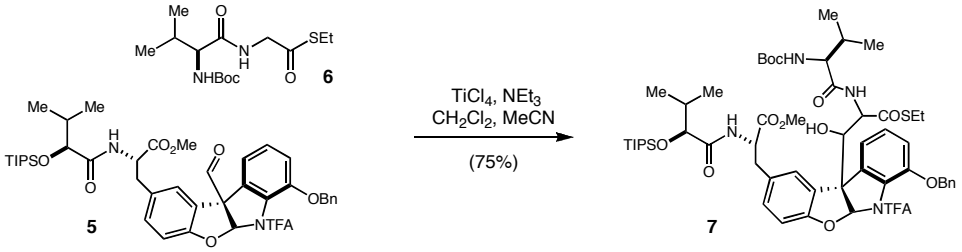
Table 1: Ring contraction thermochemistry



Entry	E (hartree)
Ketoamide	–1973.637342
Oxazole	–1897.607806
Water	–75.97396515
ΔE°	0.07557138
ΔE° (kcal)	+47.42

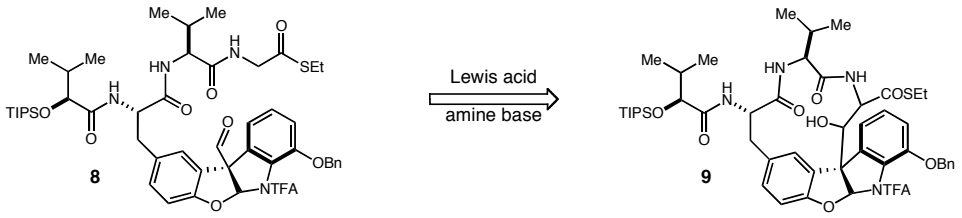
oxazole and the left-hand macrocycle of **4** in a single operation. We were hopeful that the generation of aromaticity in this process would mitigate the energetic penalties associated with the concomitant increase in ring strain (Figure 1).[3]

Intermolecular aldol employed in original approach



(3)

Proposed intramolecular variant



(4)

[2] Calculations carried out using the B3LYP functional at the 3-21G level of theory in Gaussian 03. Energy value for the oxazole form takes into account the loss of water. See supporting information for details.

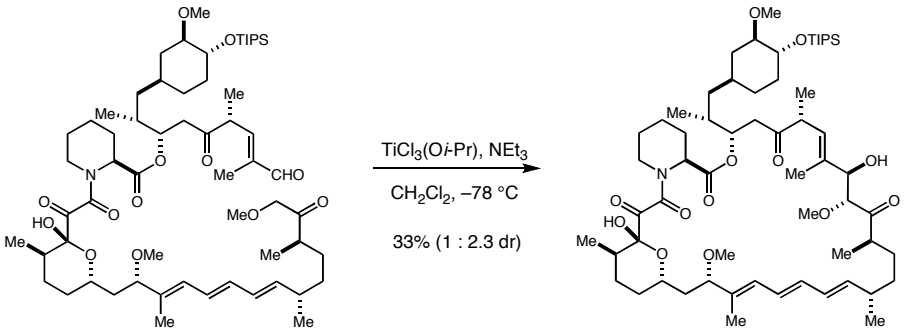
[3] For a recent example of using the generation of aromaticity to form a highly strained macrocyclic ring, see: Wipf, P.; Furegati, M. *Org. Lett.* **2006**, *8*, 1901–1904.

We envisioned that ketone **3** could be synthesized in analogy to our previous work, by oxidation of its corresponding alcohol **9** (eq 4). This alcohol could then theoretically be obtained from an intramolecular aldol annulation similar to the intermolecular variant realized in our first generation synthesis (eq 3,4).

While this aldol disconnection was very straightforward from a tactical and retrosynthetic point of view, it was much less obvious whether it would be a synthetically viable approach. Specifically, upon searching the relevant literature, we found that intramolecular aldolizations to form large rings are inauspiciously rare. The two most relevant examples in complex target synthesis were both reported by the Danishefsky group; first in the closure of a 30-membered ring in the synthesis of rapamycin (eq 5) and

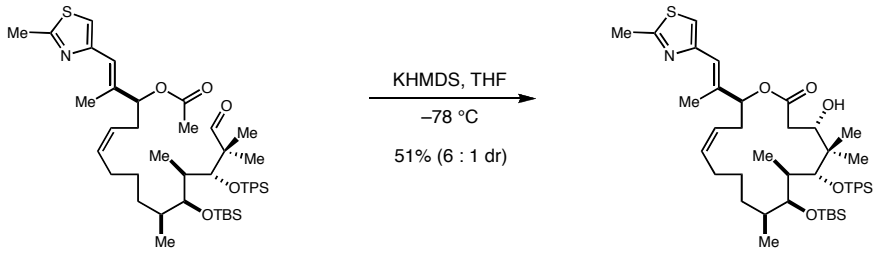
Figure 3. Intramolecular macroaldolizations in complex molecule synthesis

■ Danishefsky's rapamycin synthesis



(5)

■ Danishefsky's epothilone synthesis



(6)

then in the annulation of a 16-membered ring in the synthesis of epothilones A and B (eq 6).[4,5]

As the aldol reaction is amongst the most reliable and heavily utilized carbon-carbon bond constructions in all of synthetic chemistry, we were initially surprised to find that its application to macrocyclization was so infrequent. Yet, in order to be successful, the intramolecular variants have strict mechanistic requirements that can often be difficult to fulfill. Specifically, these transformations require selective enolization of the pro-nucleophilic carbonyl in the presence of the electrophilic aldehyde carbonyl. Due to the disparity in pK_a values between aldehydes and most other carbonyl derivatives, this becomes possible only if the nucleophile is pre-activated, as in Reformatsky-type processes, or in cases where the aldehyde is nonenolizable. Also, as other reasonably acidic sites on the substrate can interfere with productive and selective enolate formation, heteroatom-protecting groups are often required to ensure high reaction efficiency. Moreover, intermolecular aldol reactions are often kinetically competitive, requiring the use of high dilution conditions.

Fortunately, the aldehyde electrophile in intermediate **8** (eq 4) is neopentyl and nonenolizable, suggesting that its use in intramolecular aldolization may at least be possible. However, the desired thioester functionality would still have to be successfully and selectively soft-enolized in the presence of the multitude of other strongly Lewis basic sites in the substrate. Yet, we deemed that this approach was a sufficiently

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[4] Hayward, C. M.; Yohannes, D.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1993**, *115*, 9345–9346.

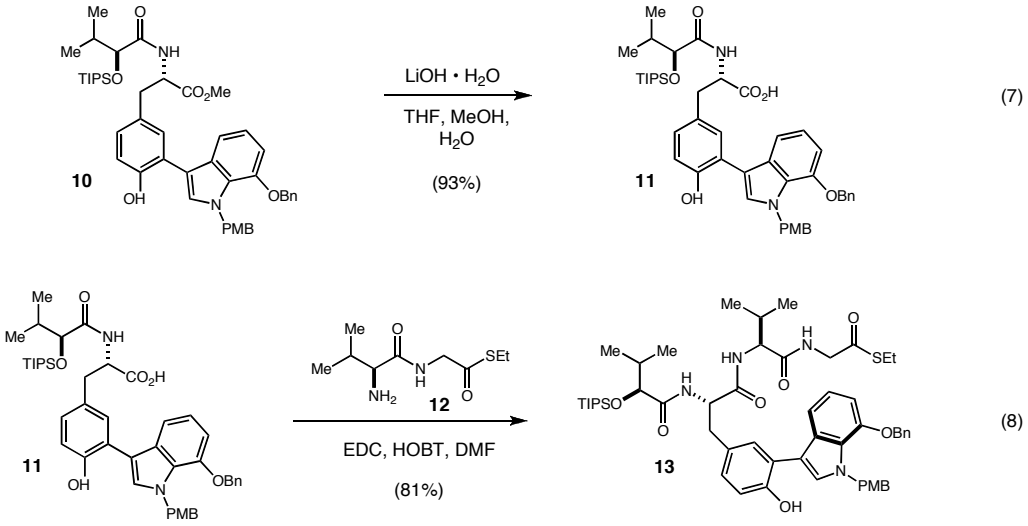
[5] Meng, D.; Bertinato, P.; Balog, A.; Su, D.; Kamenecka, T.; Sorensen, E. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1997**, *119*, 10073–10074.

compelling and original solution to this particular synthetic challenge, and we elected to pursue it in earnest.

II. Second-Generation Synthesis

In the forward sense, our new approach begins with the hydrolysis of methyl ester **10**, the synthesis of which was described in Chapter 4 (Scheme 1). The product carboxylic acid **11** was then appended to valine-glycine thioester **12** under the action of EDC and HOBT, to yield **13**, the key precursor for our organocatalytic alkylation.

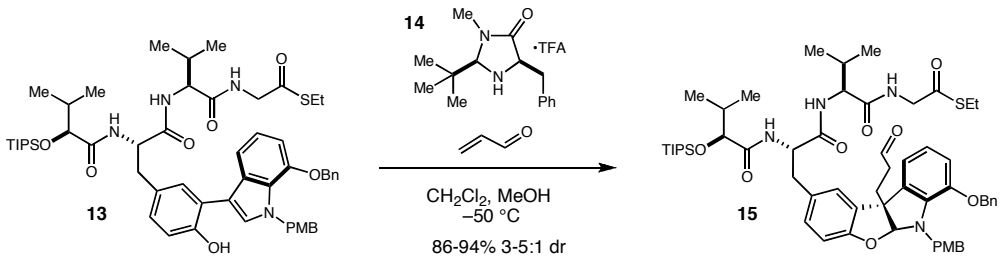
Scheme 1: Synthesis of a new organocatalytic precursor



With **13** in hand, our attention turned to the key iminium-catalyzed alkylation of acrolein. We were initially apprehensive that the appendage of the valine-glycine dimer to the organocatalytic precursor would affect the efficiency and stereoselectivity of the key iminium-catalyzed asymmetric alkylation/furanoindoline formation due to the additional steric bulk and the presence of a new, albeit distal, stereogenic center. But we were gratified to observe that, upon subjection to our optimized conditions from the

original synthetic scheme at –50 °C for 48 hours, we obtained a 94% isolated yield of the desired product **15** (Figure 4). The diastereoselectivity of this reaction proved to somewhat variable, but the range was typical of what we had observed in our previous studies, falling between 3–5:1. Notably, the use of racemic imidazolidinone catalyst **14** delivered the product as a 1:1 mixture of diastereomers, demonstrating that the stereoselectivity in the alkylation step was fully catalyst controlled.

Figure 4: Alkylation/cyclization on a more complex substrate



■ Stereoinduction at the quaternary carbon controlled by catalyst

■ Additional stereocenter has no impact on diastereoselection

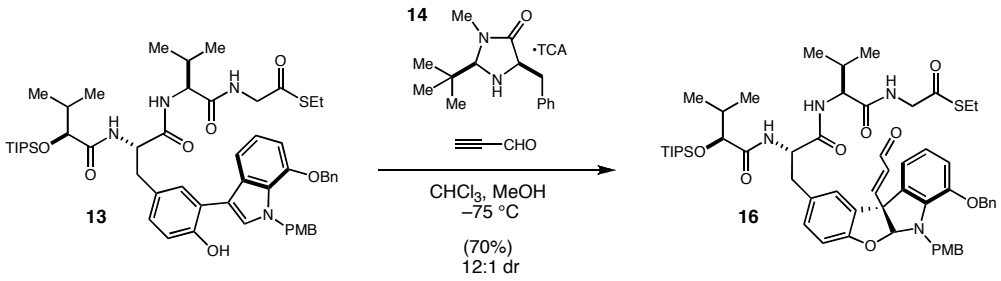
Notably, during the preparation of this thesis, Joseph Carpenter, a fellow graduate student in the MacMillan lab, discovered that treatment of **13** with propynal and the TCA salt of imidazolidinone **14** in chloroform at –75 °C results in the direct construction of α,β-unsaturated furanoindoline **16** in good yield and with an excellent 12:1 diastereoselectivity (Figure 5).[6] This result is exceptional not only in that it provides such amplified levels of stereoselectivity over the acrolein alkylation, but by directly installing the unsaturation it also reduces the overall synthetic scheme by two linear steps. The factors controlling stereoinduction in iminium ions derived from propynal were expected to be analogous to those governing additions to acrolein.[7] As such, a rationale for the

[6] Carpenter, J. E.; MacMillan, D. W. C. *Unpublished results.*

[7] For a stereochemical rationale for additions to acrolein, see Chapter 4.

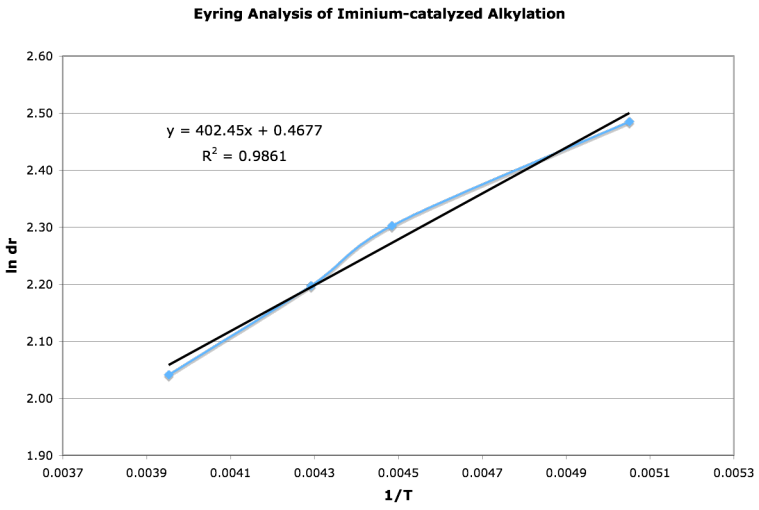
enhanced stereoselectivity has not yet been formulated, but is an area of active and ongoing investigation in the MacMillan lab.

Figure 5: Propynal alkylation proceeds with exceptional diastereoselectivity



Notably, the use of propynal allowed this alkylation reaction to be conducted at lower temperatures than were possible in the corresponding acrolein case discussed above. As such, it allowed Carpenter to methodically investigate the effect of temperature on diastereoselectivity over a much wider range of temperatures (Table 2). Subjecting this data to a standard Eyring analysis revealed a highly linear data set, implying that the factors the catalyst employs to enforce diastereoselectivity in the transition state are invariant over the entire range of temperatures investigated. This is a truly remarkable finding in the described circumstance given the strongly reactive electrophile employed

Table 2: Eyring analysis of temperature effects on diastereoselectivity



Entry	Temp °C	dr
1	–75	12:1
2	–50	10:1
3	–40	9:1
4	–20	7.7:1

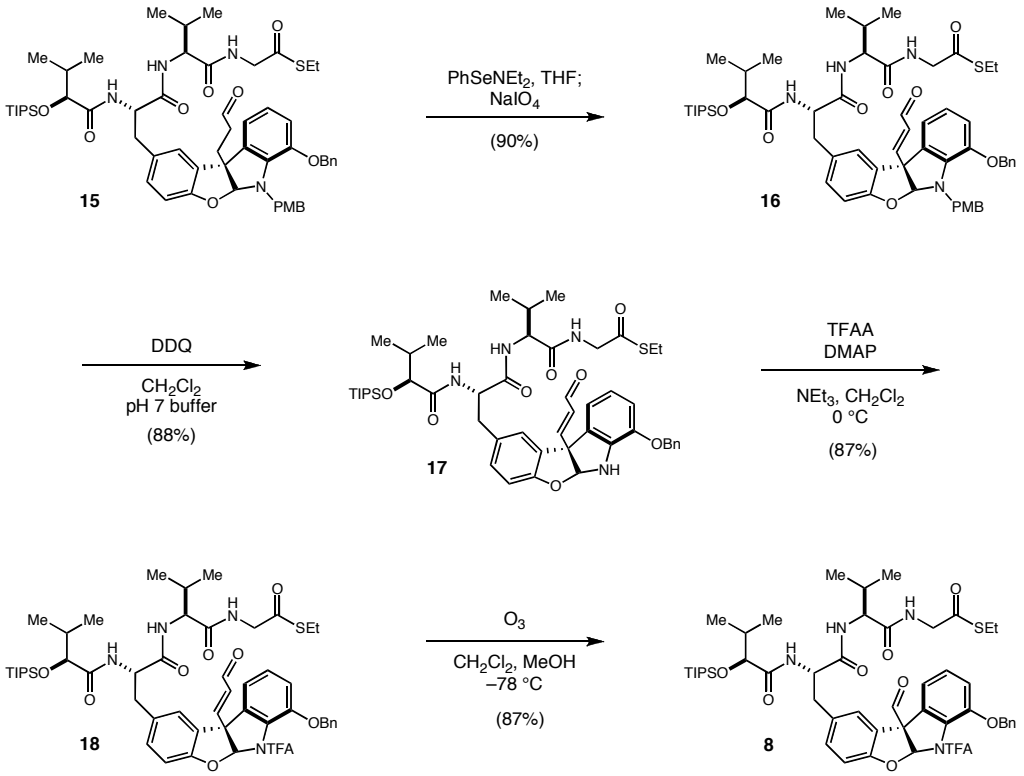
$\Delta\Delta H^{\ddagger}$ = 0.798 kcal/mol

$\Delta\Delta S^{\ddagger}$ = 0.92 cal/mol*K

and the complex nature of the large, chiral indole nucleophile. This is a strong demonstration of the degree of control the imidazolidinone catalyst can exert in transition states that engage complex substrates, and we feel confident that this bodes well for future uses of asymmetric iminium catalysis in complex and difficult natural product applications.

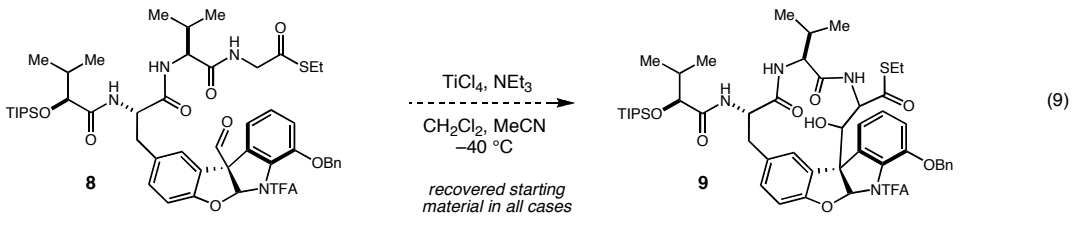
Prior to this discovery, however, saturated aldehyde **15** was processed through the same four-step sequence that had been previously developed in order to reveal the requisite aldehyde needed to investigate our aldolization reaction. Sequential, one-pot α-selenylation of **15** and oxidative elimination with $NaIO_4$ yielded α,β-unsaturated aldehyde **16** in 81% yield (Scheme 2). Subsequent treatment of **16** with DDQ in a biphasic solution of dichloromethane and pH 7 buffer oxidatively excised the indoline

Scheme 2: Elaboration of aldehyde organocatalytic adduct



PMB group to give **17** in 88% yield. The resulting aniline **17** was then reprotected as its trifluoroacetamide **18** upon treatment with TFAA and DMAP. Again, this protecting group switch was necessary to ensure the stability of the oxidizable aminal functionality towards subsequent ozonolysis, which occurred uneventfully to reveal aldehyde **18** for our proposed intramolecular aldol reaction. Remarkably, the thioester functionality remained untouched by this battery of oxidation events, undergoing no detectable oxidative decomposition.

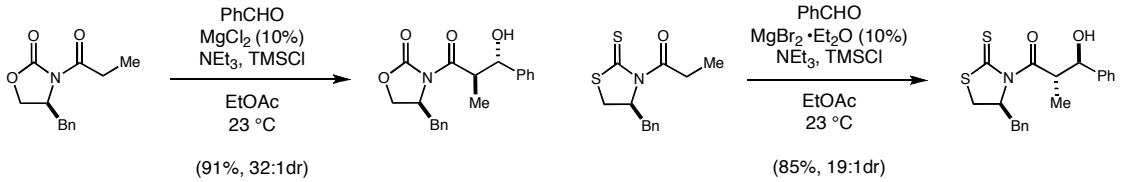
With **8** in hand, we were now positioned to begin evaluating our proposed intramolecular aldolization reaction. However, preliminary attempts using the $TiCl_4$-mediated conditions that had performed well in our previous route resulted only in recovered starting material (eq 9). Methodical modulation of all the relevant reaction parameters yielded no improvement. Previously in the intermolecular aldol, we had observed that addition of the amine base to a solution of substrate and Lewis acid produced a highly distinctive inky, blue-black solution that was indicative of the titanium enolate. Yet, no such color change was observed upon adding base to a cold solution of substrate **8** and $TiCl_4$. In fact, no color change was observed from the initial canary yellow solution. Thus, we surmised that no meaningful concentration of enolate was being formed and suspected that the titanium salt was irreversibly coordinated to any the numerous heteroatoms in the substrate, preventing effective enolization.



(9)

Pursuant to this setback, we found a particularly promising new avenue forward involving the use of magnesium-based aldol promoters. Evans and coworkers had shown that catalytic quantities of magnesium salts were capable of both effecting the soft enolization of *N*-acyloxazolidinones and *N*-acylthiazolidinethiones and mediating subsequent aldol reactions with high levels of efficiency (Figure 6).[8,9]

Figure 6: Magnesium-mediated soft enolization aldol sequences



Notably, these reactions illustrated two advantageous characteristics that we hoped to adapt to our present purpose (Figure 7). First, by virtue of being catalytic these examples illustrated that magnesium salts do not form irreversible coordination complexes with the stoichiometric amine base. Thus, we were optimistic that the many Lewis basic sites present in our substrate would not irreversibly bind the magnesium salts. Secondly, while the enolization event itself was both incomplete and reversible in these reactions, Evans showed that these aldol reactions still proceeded to full conversion. This implies that, so long as the substrate is stable to the reaction conditions, the reaction can proceed without its efficiency being predicated on achieving full and complete enolate formation. Rather, the electrophile intercepts an equilibrium content of enolate until it is fully consumed.

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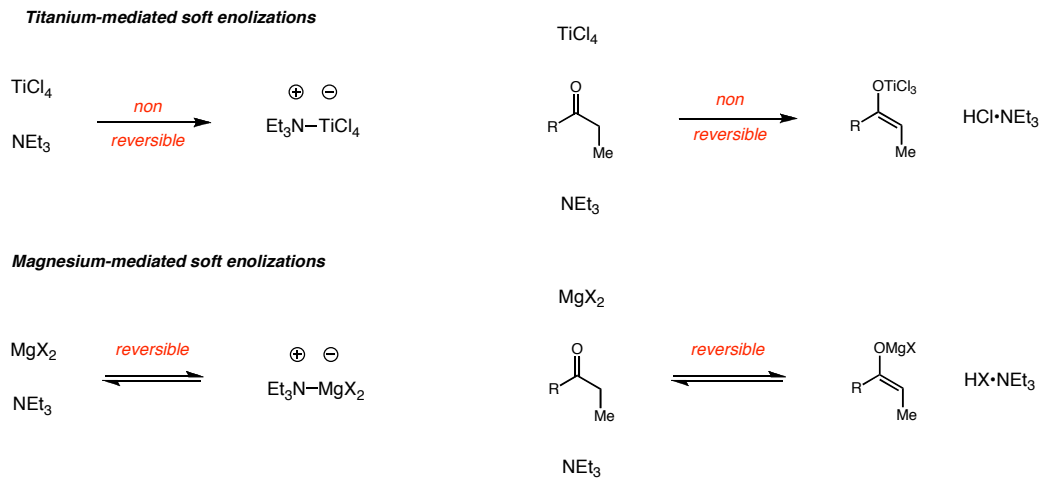
[8] For Mg-catalyzed aldol reactions with *N*-acyloxazolidinones, see: Evans, D. A.; Tedrow, J. S.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2002**, *124*, 392–392.

[9] For Mg-catalyzed aldol reactions with *N*-acylthiazolidinethiones, see: Evans, D. A.; Downey, C. W.; Shaw, J. T.; Tedrow, J. S. *Org. Lett.* **2002**, *4*, 1127–1130.

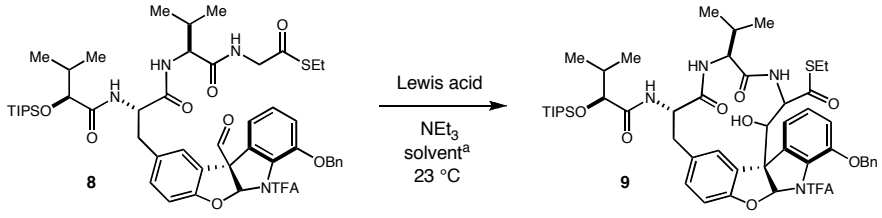
Figure 7: Advantageous equilibria in magnesium-mediated soft enolization



However, the use of magnesium also has a notable drawback. Namely, magnesium-mediated aldol reactions are often reversible. This could be especially problematic in the context of a macrocyclization, as any equilibrium that might be established would likely favor the open chain form of the starting material. However, Evans has also shown that this issue can be largely avoided by the addition of silyl chlorides to the reaction mixture. Silylation of the aldolate renders these reactions irreversible, and has the added benefit of assisting in turning over the metal salt, effectively increasing its concentration in solution to promote further enolization events.[5]

In light of these arguments, we were ecstatic to find that subjection of substrate **8** to MgBr•Et_2O and triethylamine in EtOAc at room temperature yielded 24% of the desired macroaldolization product **9** as a single diastereomer (Table 3, entry 1). This yield could be more than doubled to 51% upon addition of TMSCl to the reaction mixture (Table 3, entry 2). A small survey of solvents commonly used in soft enolization processes revealed THF to be optimal in terms of both rate and efficiency, giving a 67% yield of the desired product in under one hour at room temperature. Additionally, we

Table 3: Optimization of magneisum-mediated intramoelcular aldol macrocyclization



Entry	Lewis acid	Equivalents	Additive	Solvent	Yield %
1	$MgBr_2 \cdot Et_2O$	3	--	EtOAc	24
2	$MgBr_2 \cdot Et_2O$	10	TMSCl	EtOAc	51
3	$MgBr_2 \cdot Et_2O$	3	TMSCl	DCM	0
4	$MgBr_2 \cdot Et_2O$	3	TMSCl	THF	67
5	$MgBr_2 \cdot Et_2O$	0.3	TMSCl	THF	trace
6	MgI_2	3	TMSCl	THF	54
7	$Mg(ClO_4)_2$	3	TMSCl	THF	57
8	$Mg(OTf)_2$	3	TMSCl	THF	0

a. All reactions run at 0.004M concentration

evaluated a variety of common magnesium(II) salts, and while several were comparable, $MgBr \cdot Et_2O$ still proved optimal (Table 3, entries 6–8). The TMS-protected aldolate could be deprotected in the workup by quenching the reactions with a 1.0M HCl solution, providing direct access to the desired β-hydroxy thioester product.

There are several phenomenological aspects of this reaction that deserve further comment. When these reactions are carried out in THF, a white precipitate forms upon addition of the triethylamine base. We hypothesize that this precipitate is $NEt_3 \cdot HBr$, which is known to have limited solubility in THF. By removing these ammonium ions from solution, the equilibrium concentration of enolate should be increased, aiding the kinetics of the carbon-carbon bond-forming event. We felt this hypothesis was further bolstered by the fact that identical reactions carried out in EtOAc remained completely

homogenous throughout, but took nearly 24 hours to go to completion. Similarly, using $Mg(ClO_4)_2$ in THF gave a homogenous reaction mixture and proceeded with similar efficiency, but took nearly 12 hours to go to completion (Table 3, entry 7).

Secondly, it is notable that these reactions are operationally much less complex to carry out than typical Lewis acid-mediated aldol reactions. Specifically, they can be carried out at room temperature in solvents that have not been rigorously dried and without the use of an inert gas atmosphere, all without substantial detriment to reaction efficiency. This, coupled with the fact that $MgBr_2 \bullet Et_2O$ is an easily handled solid, makes these reactions both trivial and forgiving from a technical standpoint. The only reaction parameter that substantially affected outcomes was the quality of the $MgBr_2 \bullet Et_2O$. The best results were obtained when this reagent had been freshly prepared.

Thirdly, and most notably, in all cases examined the aldol product was exclusively formed as a single diastereomer. However, the starting material aldehyde was typically a 3.5:1 mixture of diastereomers, as the C(10) diastereomers arising from the key organocatalytic alkylation event were completely inseparable throughout the entire sequence from **15** to **8**. Given that yields of the aldol product were observed to approach 70% and that that the starting material in these reactions is always fully consumed, we postulated that the diastereomers of the starting material may be undergoing a parallel resolution. The major diastereomer was being converted with high efficiency to the desired product **9**, while the minor diastereomer was being consumed by a different reaction pathway to yield a distinct, and as of yet unidentified, byproduct. Hindered by our lack of access to each of the starting material diastereomers in pure form, this

possibility remains to be rigorously established, but it remains an active question that will be pursued in detail during future investigations.

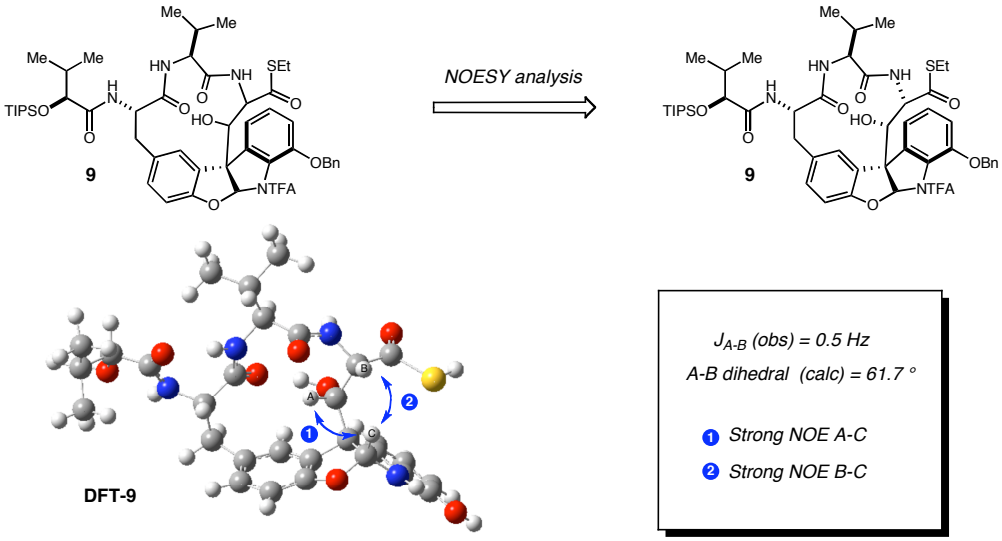
Assigning the stereochemistry of the aldol product was inconsequential to the ultimate progress of the project, as the stereocenters in questions would be destroyed in an oxidation step immediately following. Yet, in the hopes of better understanding this new aldol process and the possible reasons for the aforementioned resolution of starting material diastereomers, we were eager to evaluate the possible transition state factors that made this reaction so highly diastereoselective. Yet our initial efforts to determine the stereochemistry of **9** were hindered by our inability to convert this hindered alcohol to a corresponding pair of diastereomeric Mosher esters. Standard acylation conditions only returned starting material, while more forcing conditions resulted in decomposition believed to result from β-elimination of the hydroxy group.

In light of these failures, we attempted a stereochemical assignment based on NOESY analysis. Selected results of these experiments are presented below in Figure 8. Both the alcohol- and amine-bearing methines (protons A and B of **DFT-9** in Figure 8) exhibit cross peaks with the C(11) methine (proton C of **DFT-9** in Figure 8) in the 2-D NOESY spectrum. Moreover, the vicinal J coupling between the aldehyde and amine methines (A and B) is only 0.5 Hz, indicative of a nearly perpendicular orientation of these C-H bonds. In light of this data and the conformational constraints inherent to the macrocycle, we tentatively propose that the stereochemistry of these two centers is as shown in Figure 8.[10]

[10] The protecting groups of **DFT-9** were omitted for visual clarity and to lessen computational time.

Subsequent theoretical investigations support this view. Minimizing all four possible diastereomers of structure **9** using DFT methods provided only one structure that displayed a dihedral angle between A and B commensurate with the coupling constant as well as the proper proton proximities that could reasonably give rise to the observed NOE signals (**DFT-9**).[11]

Figure 8: NMR determination of stereochemistry for aldol product



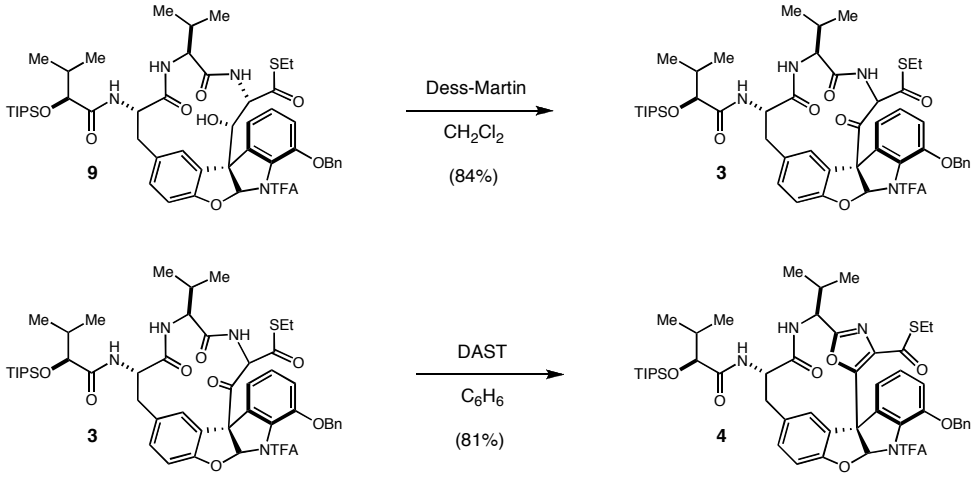
Lastly, the mildness of these reaction conditions and their success in this difficult context bodes well for the implementation of this discovery in other similar circumstances. We are hopeful that this reaction will serve as further proof that such aldolizations can be effective in the formation of large ring systems.

Following this, aldol product **9** was oxidized to its corresponding ketone under the action of Dess-Martin periodinane in good yield, providing the key intermediate **3** upon which our entire strategy hinged (Figure 9). It was entirely unclear whether our

[11] See supporting information for images of the 3-D structures, and relevant dihedral angles, of the other three DFT-minimized diastereomers.

DAST-mediated oxazole-forming conditions had any chance of success when coupled to an energetically less favorable ring contraction. However, we were extremely gratified to find that, upon subjection to our standard conditions of DAST in benzene at room temperature, we obtained the desired ring-contracted oxazole and the intact left-hand macrocycle of **4** in 81% yield. Notably, this process is markedly more efficient than the acyclic case described in Chapter 4.

Figure 9: Oxidation and cyclodehydration yield left-hand macrocycle

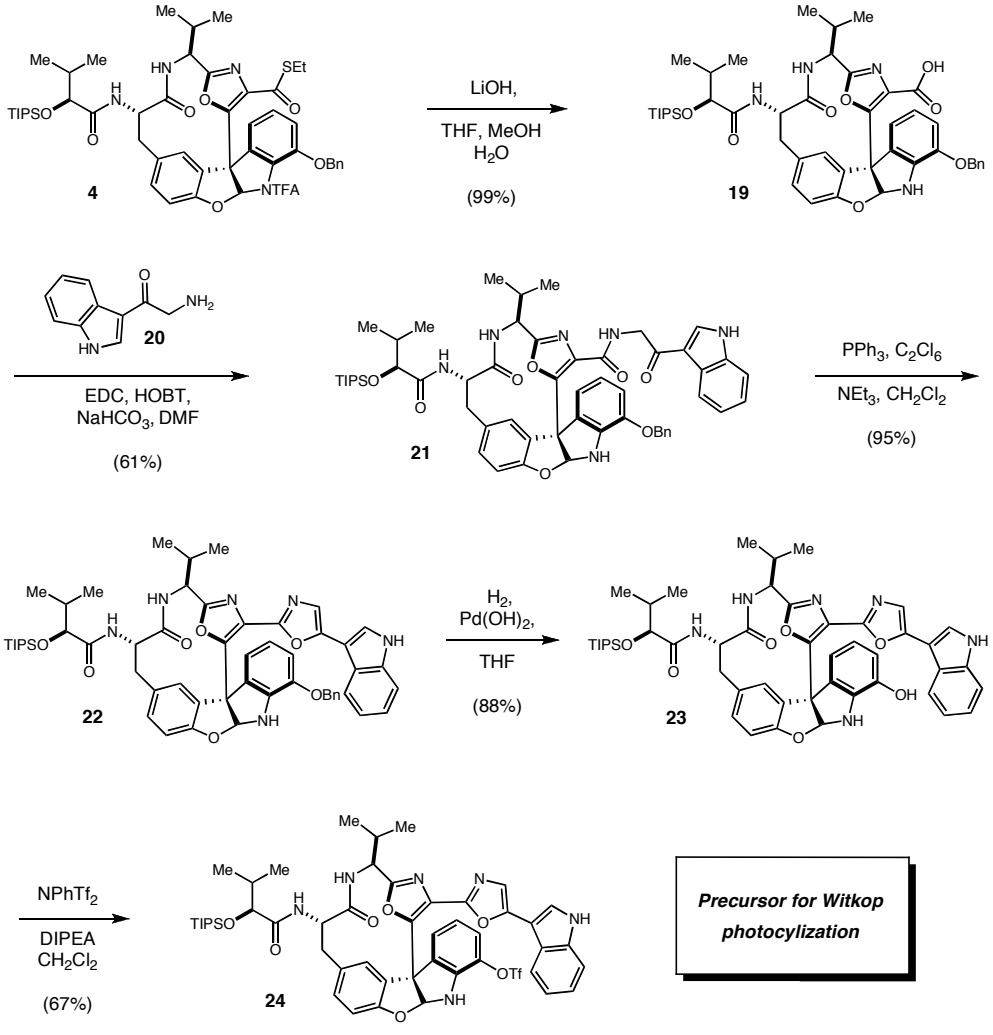


These results were especially pleasing–not only in that our iminium technology, magnesium macroaldolization, and novel oxazole-forming reaction had performed so well in such difficult circumstances–but also in that analysis of our previous failures on mechanistic grounds led to the identification of a pleasingly novel synthetic strategy that was successfully reduced to practice. Moreover, the sequence described in this chapter thus far represents successful completion of a substantial fraction of our overarching project goals. We had created a highly diastereoselective organocatalytic construction of the C(10) stereocenter and the furanoindoline core, and had devised a highly novel and efficient method to generate the left-hand macrocyclic domain. Moreover, this series of

reactions represents by far the most stereoselective access to the C(10) stereocenter, furanoindoline core and left-hand macrocycle that have yet been reported in the diazonamide literature. Now, all that remained was to affect ring closure of the right-hand macrocycle and install the aryl chlorides for our total synthesis to be completed.

We were optimistic that this would be accomplished in a straightforward manner given our prior success in closing the right-hand macrocycle using a Witkop-type arylation.[12] So, we next set out to synthesize the requisite photocyclization precursor **24**

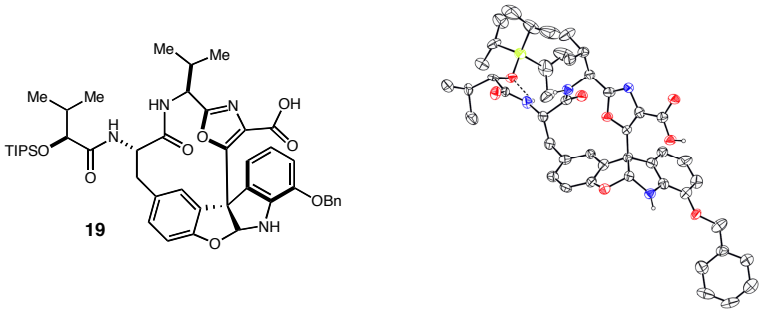
Scheme 3: Synthesis of Witkop precursor



[12] For details of our previous efforts using photocyclizations to close this ring, see Chapter 4.

(Scheme 3). Thioester **4** was first hydrolyzed to its corresponding carboxylic acid **19** with aqueous lithium hydroxide. Notably, Carpenter was able to grow X-ray quality crystals of acid **19**, proving that our series of intermediates had the correct connectivity and relative stereochemistry for the natural product (Figure 10).

Figure 10: X-ray structure proves connectivity and relative stereochemistry



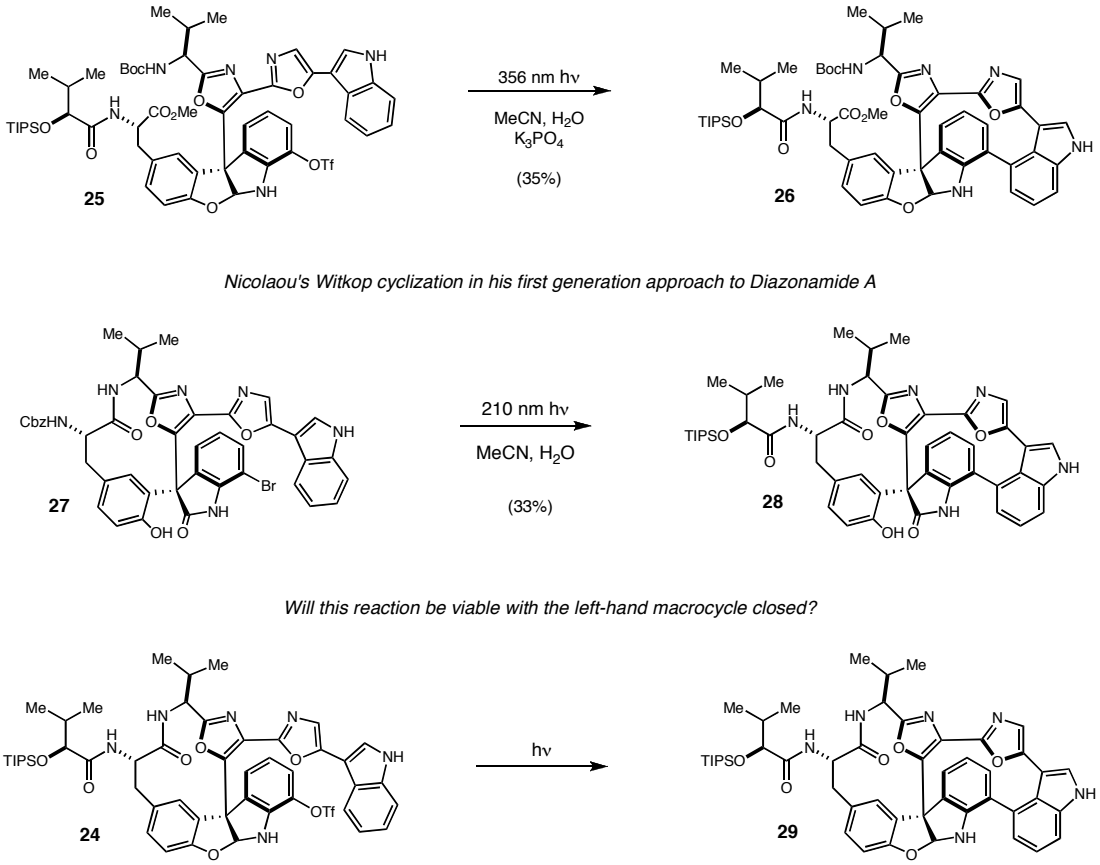
Acid **19** was then coupled to 3'-oxotryptamine **20** using standard peptide coupling protocols, giving amide **21** in an unoptimized 61% yield. This amidoketone **21** was then cyclodehydrated according to the procedure of Wipf to yield the B-ring oxazole of **22** in 95% yield.[13] Notably the success of this reaction was dependent on forming the phosphonium reagent at room temperature and then adding it portionwise to a solution of the substrate. Hydrogenolysis of the benzyl ether with Pearlman's catalyst yields phenol **23** in 88% yield. Finally, phenol **23** was treated with $NPhTf_2$ and Hunig's base in CH_2Cl_2 to yield the key aryl triflate **24**, with which we would investigate the photo-mediated annulation.

At this point we were very optimistic about our prospects for success. We had demonstrated that such reactions were feasible with triflate leaving groups in our first generation synthesis (Figure 11). Moreover, Nicolaou had carried out this type of

[13] Wipf, P.; Miller, C. P. *J. Org. Chem.* **1993**, *58*, 3604–3606.

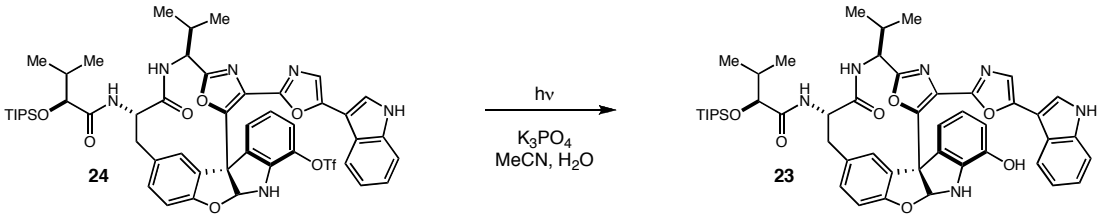
cyclization on a structurally similar aryl bromide in his first-generation synthesis of diazonamide A.

Figure 11: Photocyclizations of the right-hand macrocycle

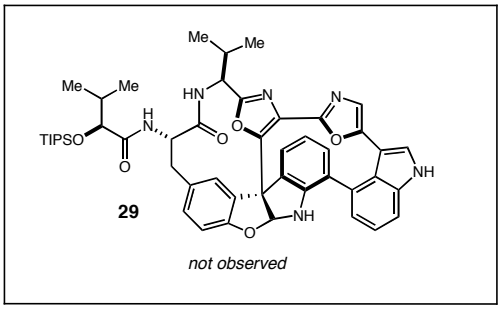


But these hopes were dashed when we exposed **24** to photolysis and did not observe any detectable cyclization (Figure 12). Evaluating a range of wavelengths and solvents yielded no improvement. Rather, all that we observed was hydrolysis of the aryl triflate to its corresponding free phenol **23**. It became apparent that having the left-hand macrocycle in place slowed the productive cyclization pathway sufficiently such that this competing hydrolysis pathway was able to exclusively consume the starting material. This was somewhat surprising, as closing the left-hand ring makes the structure very

Figure 12: Major product is the phenol resulting from triflate hydrolysis



Witkop cyclization is no longer a viable method for biaryl construction



rigid, permanently affixing the electron-rich indole donor in very close proximity to the triflate acceptor. Yet, it seemed unlikely that this situation would be easily remedied using this photo-annulation technology.

Needless to say, this was a tremendous setback, as we had again come tantalizingly close to completing the synthesis, only to witness another dramatic late-stage failure. Yet, it also compelled us to recognize that by repeating this cyclization that had been used by both Nicolaou and Harran, we were passing on a chance to contribute a novel solution to the synthesis of this daunting substructure. As such we resolved to pursue an entirely novel approach to synthesizing this challenging substructure. Our efforts toward this end are described in detail in the following chapter.

Chapter 4 Supporting Information

General Information: Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[14] All solvents were purified according to the method of Grubbs.[15] Nonaqueous reagents were transferred under argon via syringe or cannula. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator using a heated water bath. Chromatographic purification of products was accomplished using forced-flow chromatography on Silicycle 230–400 mesh silica gel 60 according to the method of Still.[16] Thin-layer chromatography (TLC) was performed on Silicycle 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by fluorescence quenching or by CAM stain.

^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 (300 MHz and 75 MHz) as noted, and are internally referenced to residual solvent signals. Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (Hz) and assignment. Data for ^{13}C NMR are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer 1000 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Mass spectra were obtained from the Caltech Mass Spectral Facility.

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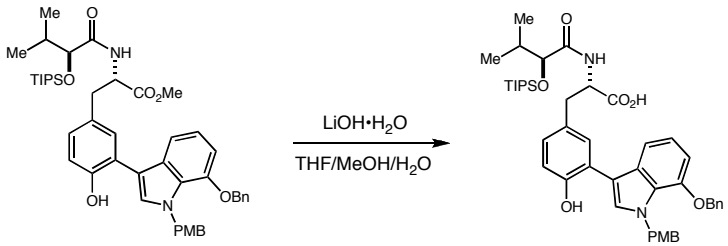
[14] Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals;* 3rd ed., Pergamon Press, Oxford, 1988.

[15] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.

[16] Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978**, *43*, 2923.

Optical rotations were measured on a Jasco P-1010 polarimeter, and $[\alpha]_D$ values are reported in 10^{-1} dg cm^2 g^{-1}.[17]

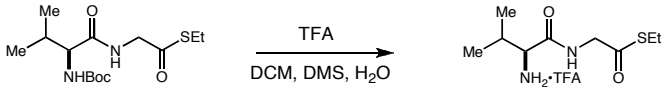


10 11

Acid 11: To a solution of **10** (9.50 g, 11.98 mmol) in THF/MeOH/H_2O (130 mL, 10:2:1) was added LiOH•H_2O (2.01 g, 47.9 mmol) with stirring. After the reaction was judged complete by TLC analysis (4 h), the reaction mixture was diluted with 300 mL of diethyl ether, acidified with 1N HCl to pH 2, and washed with 100 mL of brine. The organic portion was dried over sodium sulfate and concentrated *in vacuo*. These crude extracts were purified by column chromatography (40% EtOAc/Hexanes with 1% AcOH) to yield the title compound (8.96 g, 96%) as a white amorphous solid. IR (Film): 3402, 2944, 2867, 1723, 1641, 1613, 1572, 1513, 1454, 1385, 1248, 1209, 1176, 1063, 909, 882, 821, 732 cm^{-1}; ^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.35–6.73 (m, 17H, Ar**H** and N**H**); 5.57 (s, 2H, OC**H**$_2$Ph), 5.13 (s, 2H, OC**H**$_2$-pMeOPh), 4.89 (dd, 1H, J = 7.2, 12.9 Hz, C**H**CO_2H), 4.16 (d, 1H, J = 3.3 Hz, C**H**OTIPS); 3.76 (s, 3H, ArO**Me**); 3.17 (dd, 1H, J = 5.4, 14.7 Hz, C**H**$_2$Ar); 3.05 (dd, 1H, J = 7.2, 14.4 Hz, C**H**$_2$Ar); 1.92 (m, 1H, C**H**Me_2); 1.04–0.98 (m, 21H, TIPS); 0.83 (d, 3H, J = 6.9 Hz, CH(**Me**)Me); 0.74 (d, 3H, J = 6.9 Hz, CH(**Me**)Me); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 175.8, 173.5, 158.8, 152.6, 146.9, 136.7, 131.3, 131.1,

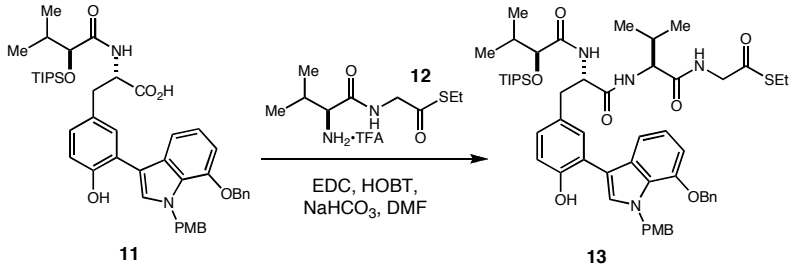
[17] Certain data herein was reproduced from the Caltech thesis of Ian K. Mangion, (2006) with whom this work was jointly carried out.

129.2, 129.1, 128.6, 128.2, 128.0, 127.8, 127.2, 126.5, 121.3, 120.9, 115.6, 113.9, 112.7, 110.9, 104.5, 78.0, 70.4, 55.2, 52.6, 52.1, 37.0, 33.9, 18.0, 17.9, 17.6, 17.2, 12.3; HRMS (FAB+) exact mass calculated for [M+•] ($C_{46}H_{58}N_2O_7Si$) requires *m/z* 778.4013, found *m/z* 778.4034 $[\alpha]_D^{25}$ = –28.48 (c = 0.53, $CHCl_3$)



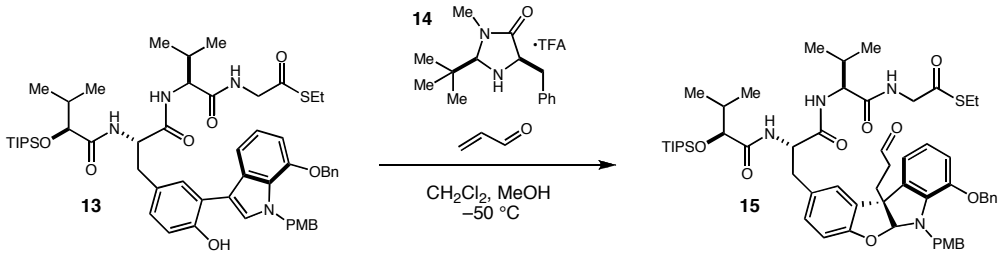
12a **12**

Thioester 12: To a solution of 300 mL of 60:7:2:1 CH_2Cl_2/TFA/Me_2S/H_2O under argon was added **12a** (7.0 g, 22 mmol). After 12 hours the solution was concentrated. The resulting oil was purified by column chromatography (10% MeOH/CH_2Cl_2) to yield the title compound as a white crystalline solid in 90% yield (6.24 g). IR(Thin Film): 2972, 2941, 1668, 1471, 1202, 1181, 1137, 971, 838, 799, 722 cm^{-1}; ^1H NMR: (300 MHz, CD_3OD) δ 4.28 (d, 1H, J = 17.4 Hz, NHC**H**$_2$), 4.06 (d, 1H, J = 17.4 Hz, NHC**H**$_2$), 3.77 (d, 1H, J = 5.7 Hz, C**H**NH_2), 2.91 (q, 2H, J = 7.5 Hz, SC**H$_2$**), 2.25 (m, 1H, C**H**Me(Me)), 1.23 (t, 3H, J = 7.5 Hz, SCH_2**CH_3**), 1.10 (d, 3H, J = 6.9 Hz, CH**Me**(Me)), 1.07 (d, 3H, J = 6.9 Hz, CHMe(**Me**)); ^{13}C NMR: (75 MHz, CD_3OD) δ 196.8, 169.0, 156.2, 58.5, 30.3, 22.7, 17.7, 16.6, 13.9; HRMS: (FAB+) exact mass calculated for [M+H] ($C_9H_{19}N_2O_2S$) requires *m/z* 219.1167, found *m/z* 219.1171; $[\alpha]_D^{25}$ = –0.95 (c = 1.0 MeOH)



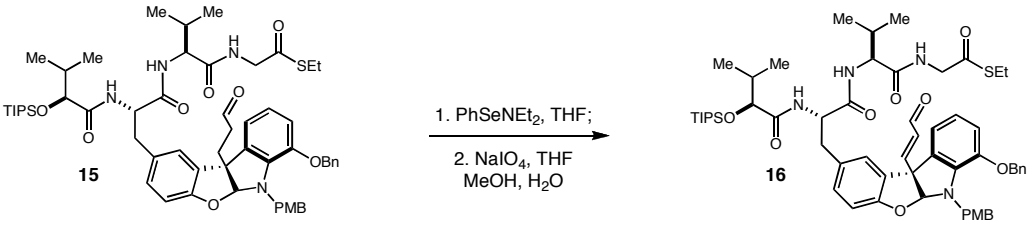
Thioester 13: To a solution of **11** (8.96 g, 11.5 mmol) and **12** (4.71 g, 15.0 mmol) in DMF (120 mL) was added HOBt (2.02 g, 15.0 mmol), EDC•HCl (2.87 g, 15.0 mmol), and $NaHCO_3$ (3.86 g, 46.0 mmol) with stirring. After the reaction was judged complete by TLC analysis (7 hours), the reaction mixture was diluted with 500 mL of diethyl ether and washed with 200 mL of saturated NH_4Cl, H_2O, and brine. The organic portion was dried over sodium sulfate and concentrated *in vacuo*. These crude extracts were purified by column chromatography (40% EtOAc/hexanes) to yield the title compound (10.7 g, 95% yield) as a white amorphous solid. IR (Film): 3288, 2962, 2943, 2868, 1642, 1612, 1513, 1455, 1385, 1262, 1248, 1209, 1176, 1064, 909, 882, 823, 732 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ 7.35–6.49 (m, 19H, Ar**H** and N**H**); 5.57 (s, 2H, OC**H**$_2$Ph); 5.15 (s, 2H, OC**H**$_2$-pMeOPh); 4.62 (dd, 1H, J = 7.2, 12.9 Hz, CH_2C**H**CONH); 4.30 (dd, 1H, J = 5.6, 8.6 Hz, NHC**H**$CHMe_2$); 4.16 (d, 1H, J = 3.0 Hz, C**H**OTIPS); 3.98 (t, 2H, J = 4.8 Hz, NHC**H**$_2$); 3.76 (s, 3H, ArO**Me**); 3.08 (m, 2H, C**H**$_2$Ar); 2.82 (q, 2H, J = 7.5 Hz, SC**H**$_2$); 2.21 (m, 1H, NHCHC**H**Me_2); 1.92 (m, 1H, OCHC**H**Me_2); 1.19 (t, 3H, J = 7.5 Hz, SCH_2**C**H_3); 1.04–0.98 (m, 21H, TIPS); 0.89–0.83 (m, 9H, OCHCH(**Me**)Me, NHCHCH(**Me**)**Me**); 0.74 (d, 3H, J = 6.9 Hz, OCHCH(**Me**)Me); ^{13}C NMR: (300 MHz, $CDCl_3$) δ 196.9, 173.8, 171.0, 170.9, 158.8, 152.5, 146.9, 136.7, 131.2, 131.0, 128.9, 128.6, 128.3, 128.1, 127.8, 127.7, 126.5, 121.7, 120.9, 115.7, 113.9, 112.7, 110.8, 104.6, 78.0, 70.4, 58.5, 55.2, 54.8, 52.2, 48.9, 37.2, 34.0, 29.8, 23.0, 19.4, 18.0, 17.5, 17.0, 14.5,

12.4; HRMS (FAB+) exact mass calculated for [M+•] ($C_{55}H_{74}N_4O_8SiS$) requires *m/z* 978.4996, found *m/z* 978.4966; $[\alpha]_D^{25} = -17.13$ (c = 2.18, $CHCl_3$).



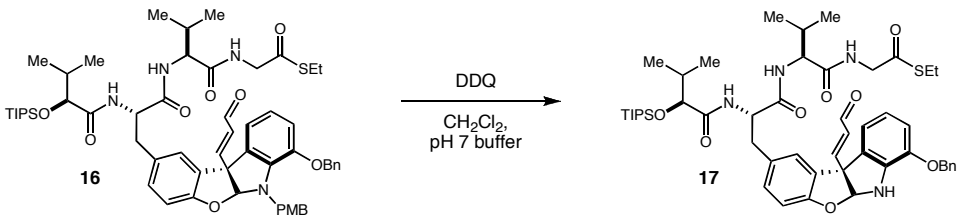
Aldehyde 15: (2*R,5R*)-2-*tert*-butyl-5-benzyl-3-methylimidazolidin-4-one•TFA **14** (1.03 g, 2.86 mmol) and phenol **13** (8.0 g, 8.17 mmol) are dissolved in 40 mL of dichloromethane and 2 mL of MeOH. This mixture is cooled to –50 °C. To this cold solution is added freshly distilled acrolein (5.51 mL, 81.7 mmol). The reaction is left for 48 hours at –50 °C before being diluted with 50 mL of pH 7 buffer. The layers were separated and the organic portions were washed with brine and dried over sodium sulfate. Following concentration *in vacuo*, the crude reaction extracts were purified by flash chromatography (80% Et_2O in pentane) to afford the title compound as an amorphous white solid (7.9 g, 93%). IR (Film): 3408, 3300, 2962, 2942, 2868, 1720, 1648, 1512, 1495, 1466, 1386, 1247, 1175, 1100, 1065, 915, 882, 822, 733, 683 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ 9.45 (s, 1H, C**H**O); 7.36–6.44 (m, 15H, Ar-**H**); 5.80 (s, 1H, OC**H**N); 5.33 (d, 1H, J = 15.6 Hz, NC**H$_2$**-pMeOPh); 5.01 (m, 2H, OC**H$_2$**Ph); 4.60 (m, 2H, C**H**NHCO); 4.47 (d, 1H, J = 15.6 Hz, NC**H$_2$**-pMeOPh); 4.26–3.94 (m, 3H, C**H**OTIPS, NHC**H$_2$**); 3.78 (s, 3H, ArO**Me**); 3.11–2.80 (m, 4H, C**H$_2$**Ar, SC**H$_2$**); 2.29–1.84 (m, 6H, NHCHC**H**Me_2, OCHC**H**Me_2, C**H$_2$**C**H$_2$**CHO); 1.21 (t, 3H, J = 7.5 Hz, SCH_2**CH$_3$**); 1.09–

0.68 (m, 33H, TIPS, OCHCH(**Me**)Me, NHCHCH(**Me**)**Me)**; ^{13}C NMR: (300 MHz, $CDCl_3$) δ 201.0, 196.6, 173.9, 173.6, 170.9, 170.8, 170.7, 158.8, 157.8, 152.5, 146.9, 137.0, 136.7, 133.3, 132.5, 130.1, 130.8, 129.4, 129.3, 129.0, 128.8, 128.6, 128.5, 128.1, 128.0, 127.9, 127.5, 126.5, 123.6, 121.0, 120.4, 115.6, 114.0, 113.4, 110.7, 109.9, 105.8, 104.6, 78.0, 70.9, 58.5, 57.8, 55.3, 54.8, 50.4, 49.0, 39.0, 33.9, 29.9, 29.3, 23.1, 19.2, 18.1, 18.0, 17.6, 17.0, 14.6, 12.4; HRMS (FAB+) exact mass calculated for [M+H] ($C_{58}H_{78}N_4O_9SiS$) requires *m/z* 1034.526, found *m/z* 1034.528; $[\alpha]_D^{25}$ = –35.94 (c = 1.0, $CHCl_3$).



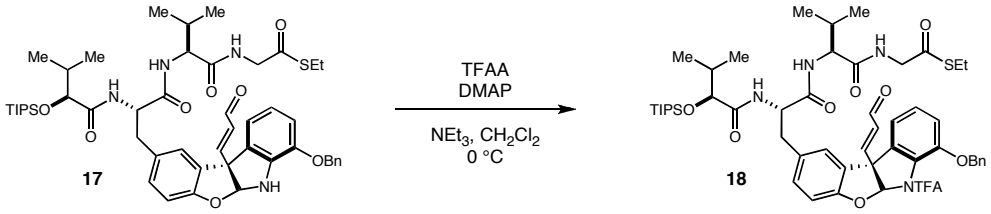
Aldehyde 16: To a solution of aldehyde **15** (5.73 g, 5.53 mmol) in 70 mL of THF at room temperature was added $PhSeNEt_2$ (1.47 mL, 7.65 mmol). After stirring for one hour the reaction was judged complete by TLC. The reaction mixture was concentrated *in vacuo* and the crude extracts were purified by flash chromatography (33% EtOAc in hexanes). The product was thus obtained as a yellow oil in a 3:3:1:1 mixture of diastereomers as judged by ^{1}H-NMR. This product was then taken up in 42 mL of THF, 21 mL of methanol, and 21 mL of water. To this solution was added sodium periodate (2.06 g, 9.62 mmol) in a single portion. After 12 hours the reaction mixture was concentrated *in vacuo* to remove the methanol and THF, diluted with ethyl acetate, and washed with water. After separation of the layers the organic portions were washed with

brine and dried over sodium sulfate. Concentration of the resulting solution gave a yellow oil which could be purified by column chromatography (33% EtOAc in hexanes) to give the title compound as an amorphous off-white solid (4.81 g, 84%). IR (Film): 3409, 3300, 2962, 2942, 2868, 1692, 1648, 1512, 1494, 1466, 1385, 1248, 1175, 1100, 1064, 973, 911, 882, 822, 733, 683 cm^{-1}; ^{1}H NMR: (300 MHz, $CDCl_3$) δ 9.45 (d, 1H, J = 7.5 Hz, C**H**O); 7.33–6.72 (m, 16H, Ar-**H**, C**H**=**C**HCHO); 6.46 (d, 1H, J = 8.1 Hz, CON**H**); 5.93 (s, 1H, OC**H**N); 5.88 (dd, 1H, J = 15.9, 7.8 Hz, CH=**CH**CHO); 5.22 (d, 1H, J = 15.3 Hz, NC**H_2**-pMeOPh); 5.01 (m, 2H, OC**H_2**Ph); 4.59–4.46 (m, 3H, C**H**NHCO, NC**H_2**-pMeOPh); 4.23 (dd, 1H, J = 8.2, 5.8 Hz, NHC**H_2**); 4.15 (d, 1H, J = 3.3 Hz, C**H**OTIPS); 4.03 (dd, 1H, J = 5.8, 1.0 Hz, NHC**H_2**); 3.76 (s, 3H, ArO**Me**); 3.11–2.82 (m, 4H, C**H_2**Ar, SC**H_2**); 2.18 (m, 1H, NHCHC**H**Me_2); 1.95 (m, 1H, OCHC**H**Me_2); 1.22 (t, 3H, J = 7.5 Hz, SCH_2C**H_3**); 1.05 (m, 21H, TIPS); 0.90–0.83 (m, 9H, OCHCH(**Me**)Me, NHCHCH(**Me**)**Me**); 0.71 (d, 3H, J = 6.9 Hz, OCHCH(**Me**)Me); ^{13}C NMR: (300 MHz, $CDCl_3$) δ 196.8, 196.6, 193.3, 173.8, 173.4, 171.0, 170.7, 158.9, 158.1, 155.3, 152.5, 146.9, 145.2, 137.3, 136.6, 136.5, 133.0, 131.8, 131.2, 130.3, 129.9, 129.7, 129.2, 129.0, 128.3, 128.0, 127.8, 127.5, 126.5, 121.7, 121.3, 121.0, 116.9, 115.7, 114.0, 113.9, 113.6, 112.7, 110.8, 110.3, 107.0, 104.6, 78.0, 70.8, 70.4, 61.6, 58.5, 55.2, 54.8, 51.1, 49.0, 37.5, 33.9, 30.3, 23.1, 19.3, 18.1, 17.5, 17.0, 14.6; HRMS (FAB+) exact mass calculated for [M+H] ($C_{58}H_{77}N_4O_9SiS$) requires *m/z* 1033.518, found *m/z* 1033.518; $[\alpha]_D^{25}$ = –46.19 (c = 1.20, $CHCl_3$).



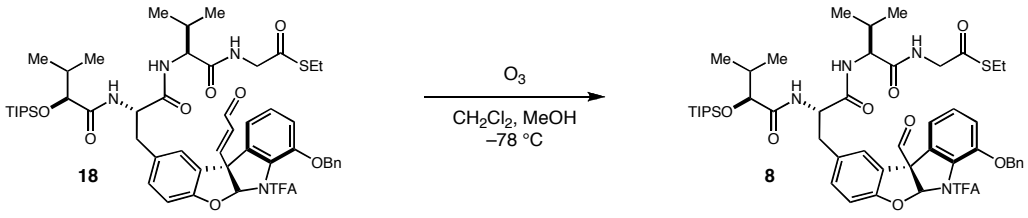
Amine 17: To a vigorously stirred solution of aldehyde **16** (4.8 g, 4.64 mmol) in a 1:1 mixture of dichloromethane and pH 7 buffer (75 mL each) at 0 °C was added freshly recrystallized DDQ (2.10 g, 9.29 mmol). The resulting dark heterogeneous reaction mixture is allowed to warm to ambient temperature over the course of two hours, after which time it is diluted with ethyl acetate and washed with a saturated solution of Na_2SO_3, followed by a saturated solution of $NaHCO_3$ and brine. The layers were separated and the aqueous layer wash washed with three times with 50 mL of ethyl acetate. The combined organic layer was washed with brine and dried over sodium sulfate. Purification by flash chromatography on silica gel (35%–40% EtOAc in hexanes) gave the desired product as an amorphous off-white solid in 84% yield (3.54 g). IR (Film): 3301, 2962, 2942, 2868, 1691, 1648, 1498, 1466, 1387, 1206, 1058, 975, 882, 823, 749, 683 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ 9.61 (d, 1H, J = 7.5 Hz, C**H**O); 7.41–6.67 (m, 12H, Ar-**H**, C**H**=**C**HCHO); 6.56 (d, 1H, J = 8.7 Hz, CON**H**); 6.24 (d, 1H, J = 2.4 Hz, OC**H**N); 6.14 (dd, 1H, J = 15.6, 7.5 Hz, CH=**C**H**C**HO); 5.04 (s, 2H, OC**H₂**Ph); 4.59 (m, 1H, CONHC**H**CH); 4.24 (dd, 1H, J = 8.6, 5.6 Hz, NHC**H₂**); 4.14 (m, 1H, CONHC**H**CH_2); 4.03 (d, 1H, J = 5.7 Hz, C**H**OTIPS); 3.93 (m, 1H, NHC**H₂**); 3.15–2.80 (m, 4H, C**H₂**Ar, SC**H₂**); 2.17 (m, 1H, NHCHC**H**Me_2); 1.92 (m, 1H, OCHC**H**Me_2); 1.22 (t, 3H, J = 7.5 Hz, SCH_2**C**H_3); 1.05 (m, 21H, TIPS); 0.90–0.82 (m, 9H, OCHCH(**Me**)Me, NHCHCH(**Me**)**Me**); 0.72 (d, 3H, J = 6.9 Hz, OCHCH(**Me**)Me); ^{13}C NMR: (300 MHz, $CDCl_3$) δ 196.6, 193.5, 173.3, 170.7, 170.4, 158.2, 155.4, 137.1, 136.6, 133.1, 130.2,

129.7, 129.5, 129.4, 129.3, 129.2, 128.6, 128.1, 127.6, 125.0, 121.0, 116.4, 112.3, 110.4, 103.0, 78.0, 70.4, 63.7, 58.5, 54.6, 49.0, 37.5, 33.9, 30.3, 23.1, 19.0, 18.1, 18.0, 17.9, 17.5, 17.0, 14.6, 12.4; HRMS (FAB+) exact mass calculated for [M+H] ($C_{50}H_{69}N_4O_8SiS$) requires *m/z* 913.4605, found *m/z* 913.4632; $[\alpha]_D^{25} = -61.30$ (c = 3.08, $CHCl_3$).



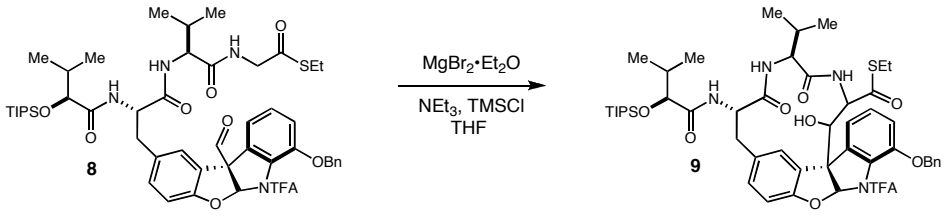
Aldehyde 18: To a solution of amino aldehyde **17** (3.54 g, 3.87 mmol), pyridine (0.78 mL, 9.68 mmol) and DMAP (165 mg, 1.35 mmol) in 77 mL of dichloromethane at 0 °C was added trifluoroacetic anhydride (0.82 mL, 5.81 mmol) dropwise by syringe under argon. After 30 minutes the reaction was diluted with 200 mL of ethyl acetate and washed with 60 mL of saturated sodium bicarbonate solution. The layers were separated and the organic fraction was washed with brine and dried over sodium sulfate. Purification by flask chromatography on silica gel (40% ethyl acetate in hexanes) gave the title compound product as an amorphous yellow solid in 87% yield (354 mg). IR (Film): 3406, 3306, 2962, 2868, 1731, 1695, 1650, 1492, 1463, 1387, 1292, 1204, 1183, 1154, 1058, 981, 882, 823, 738, 684 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ 9.65 (d, 1H, J = 7.2 Hz, C**H**O); 7.47–6.54 (m, 13H, Ar-**H**, C**H**=**C**HCHO, OC**H**N); 6.24 (dd, 1H, J = 15.9, 7.2 Hz, CH=**CH**CHO); 5.19 (dd, 2H, J = 18.6, 6.4 Hz, OC**H₂**Ph); 4.59 (m, 1H, CONHC**H**CH); 4.24–4.03 (m, 4H, NHC**H₂**, C**H**OTIPS, CONHC**H**CH_2); 3.12–2.86 (m, 4H, C**H₂**Ar, SC**H₂**); 2.13 (m, 1H, NHCHC**H**Me_2); 1.95 (m, 1H, OCHC**H**Me_2); 1.23 (t,

3H, J = 7.5 Hz, $SCH_2\mathbf{CH_3}$); 1.05 (m, 21H, TIPS); 0.90–0.86 (m, 9H, OCHCH(**Me**)Me, NHCHCH(**Me**)**Me**); 0.75 (d, 3H, J = 6.6 Hz, OCHCH(**Me**)Me); ^{13}C NMR: (300 MHz, $CDCl_3$) δ 196.2, 192.7, 173.2, 170.5, 170.1, 157.3, 151.6, 149.6, 136.3, 135.2, 131.0, 130.8, 129.2, 128.6, 128.2, 128.0, 127.0, 124.9, 116.3, 114.4, 110.5, 100.4, 78.0, 70.8, 63.3, 58.5, 54.4, 49.0, 37.6, 33.9, 30.6, 23.1, 18.9, 18.1, 18.0, 17.5, 17.1, 14.6, 12.4; ^{19}F NMR: (75 MHz, $CDCl_3$) δ –70.0 (s, 3F, CF_3); HRMS (FAB+) exact mass calculated for [M+H] ($C_{52}H_{68}N_4O_9F_3SiS$) requires *m/z* 1009.443, found *m/z* 1009.444; $[\alpha]_D^{25}$ = –133.69 (c = 0.37, $CHCl_3$).



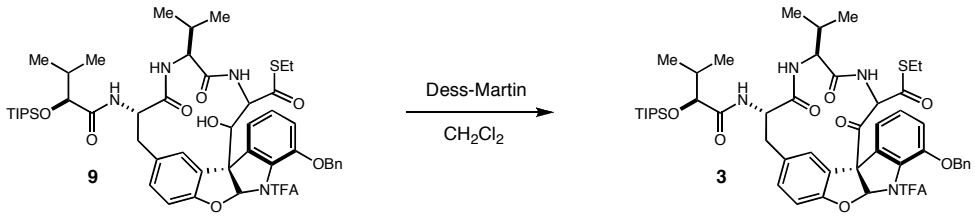
Aldehyde 8: A stream of ozone is passed through a solution of α,β-unsaturated aldehyde **18** (601 mg, 0.59 mmol) in 14 mL of dichloromethane and 1.4 mL of methanol at –78 °C for 45 minutes. The solution was bubbled through with oxygen for ten minutes and then quenched by the addition of triphenylphospine (0.44 g, 1.67 mmol). After warming to room temperature overnight the reaction mixture was concentrated *in vacuo* and loaded directly onto a silica gel column. Elution with 35% ethyl acetate in hexanes gives 517 mg of title product (88%) as an amorphous white solid. IR (Film): 3301, 2963, 2868, 1729, 1649, 1492, 1464, 1406, 1292, 1252, 1204, 1182, 1159, 985, 882, 823, 738, 684 cm^{-1}; ^{1}H NMR: (300 MHz, $CDCl_3$) δ 10.1 (s, 1H, C**H**O); 7.46–6.42 (m, 12H, Ar-**H**, OC**H**N); 5.18 (dd, 2H, J = 17.7, 12.0 Hz, $OC\mathbf{H_2}Ph$); 4.59 (m, 1H, CONHC**H**CH); 4.24–3.96 (m, 4H,

NHC**H₂**, C**H**OTIPS, CONHC**H**CH_2); 3.14–2.87 (m, 4H, C**H₂**Ar, SC**H₂**); 2.14 (m, 1H, NHCHC**H**Me_2); 1.92 (m, 1H, OCHC**H**Me_2); 1.24 (t, 3H, J = 7.5 Hz, SCH_2**C**H_3); 1.04 (m, 21H, TIPS); 0.93–0.84 (m, 9H, OCHCH(**Me**)Me, NHCHCH(**Me**)**Me**); 0.69 (d, 3H, J = 6.6 Hz, OCHCH(**Me**)Me); ^{13}C NMR: (300 MHz, $CDCl_3$) δ 196.4, 191.7, 173.4, 170.6, 170.4, 156.7, 149.5, 136.2, 132.1, 131.4, 130.7, 129.0, 128.5, 128.0, 127.0, 125.2, 124.0, 115.7, 115.0, 114.0, 110.8, 100.0, 78.0, 70.8, 58.6, 54.4, 49.0, 37.5, 33.9, 30.4, 23.2, 19.2, 18.0, 17.9, 17.8, 17.5, 17.0, 14.6, 12.3; ^{19}F NMR: (75 MHz, $CDCl_3$) δ –70.3 (s, 3F, CF_3); HRMS (FAB+) exact mass calculated for [M+H] ($C_{50}H_{66}N_4O_9F_3SiS$) requires *m/z* 983.4272, found *m/z* 983.4238; $[\alpha]_D^{25}$ = –93.42 (c = 0.47, $CHCl_3$).



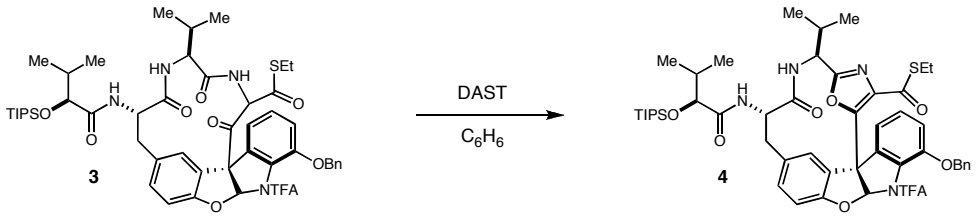
Alcohol 9: A flame-dried 1000 mL flask is charged with **8** (2.1 g, 2.14 mmol) and $MgBr_2$•Et_2O (1.65 g, 6.41 mmol) under Ar. To this flask is added THF (425 mL) followed by Et_3N (2.98 mL, 21.4 mmol) and TMSCl (0.68 mL, 5.34 mmol) with stirring. After 75 minutes 1N HCl (100 mL) is added and stirred for 10 minutes. The solution was diluted with EtOAc and pH 7 buffer, and washed with brine. The organic fractions were concentrated and the resulting oil purified by column chromatography (33% ethyl acetate in hexanes) to afford 1.49 g of the title compound (67%) as an off-white solid. IR (Film): 3401, 2962, 2868, 1732, 1681, 1644, 1490, 1462, 1288, 1204, 1181, 1160, 1125, 1099, 1057, 982, 881, 832, 752, 736, 684 cm^{-1}; ^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.50–6.86 (m,

10H, Ar-**H**); 6.77 (d, 1H, J = 8.4 Hz, Ar-**H**); 6.63 (s, 1H, OC**H**N); 5.36 (d, 1H, J = 10.2 Hz, CON**H**); 5.16 (dd, 2H, J = 17.7, 12.3 Hz, OC**H$_2$**Ph); 4.89 (d, 1H, J = 9.3 Hz, C**H**C(O)SEt); 4.48 (d, 1H, J = 6.0 Hz, C**H**OH); 4.36 (m, 1H, CONHC**H**CH); 4.18–4.10 (m, 2H, C**H**OTIPS, CONHC**H**CH$_2$); 3.04 (dd, 1H, J = 12.3, 4.6 Hz, C**H$_2$**Ar); 2.85 (q, 2H, J = 7.5 Hz, SC**H$_2$**CH$_3$); 2.65 (t, 1H, J = 12.3 Hz, C**H$_2$**Ar); 2.05 (m, 1H, NHCHC**H**Me$_2$); 1.92 (m, 1H, OCHC**H**Me$_2$); 1.20 (t, 3H, J = 7.5 Hz, SCH$_2$C**H$_3$**); 1.06–0.94 (m, 30H, TIPS, OCHCH(**Me**)Me, NHCHCH(**Me**)**Me**); 0.84 (d, 3H, J = 6.6 Hz, OCHCH(**Me**)Me); ^{13}C NMR: (300 MHz, $CDCl_3$) δ 199.8, 172.3, 170.4, 169.9, 158.6, 149.4, 136.7, 136.4, 129.8, 129.7, 128.5, 128.4, 128.3, 127.9, 127.3, 127.1, 126.4, 126.2, 117.9, 114.2, 110.9, 97.8, 77.9, 72.5, 70.8, 64.6, 58.9, 55.8, 40.2, 33.8, 30.1, 23.9, 19.3, 18.2, 18.0, 17.9, 17.8, 17.6, 17.5, 14.2, 12.2; ^{19}F NMR: (75 MHz, $CDCl_3$) δ –69.7 (s, 3F, CF_3); HRMS (FAB+) exact mass calculated for [M+H] ($C_{50}H_{66}N_4O_9F_3SiS$) requires *m/z* 983.4272, found *m/z* 983.4243; $[\alpha]_D^{25} = -129.17$ (c = 0.27, $CHCl_3$).



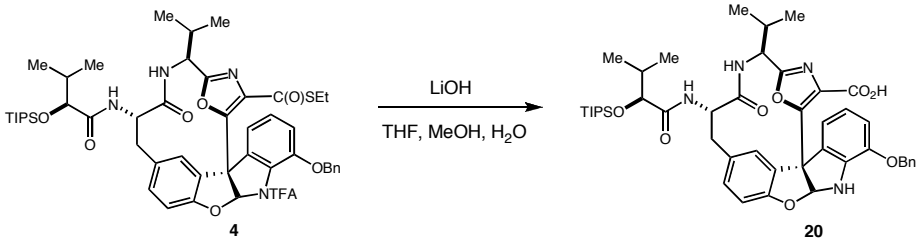
Ketone 3: To a solution of **9** (46 mg, 0.047 mmol) in 1.0 mL of CH_2Cl_2 was added Dess-Martin periodinane (59 mg, 0.14 mmol). After 30 minutes the solution was diluted with EtOAc and washed with a saturated solution of $NaHCO_3$. The organic fractions were concentrated and the resulting oil purified by column chromatography to afford 37 mg of the title compound (80%) as an off-white solid. IR (Film): 3408, 3272, 2925, 2868, 1735,

1651, 1516, 1492, 1465, 1293, 1204, 1184, 1163, 1057, 967, 881, 737, 682 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ 7.56–6.78 (m, 12H, Ar-**H**, OC**H**N); 5.76 (m, 2H, CON**H,** C**H**C(O)SEt); 5.16 (dd, 2H, J = 18.3, 12.3 Hz, OC**H₂**Ph); 4.45 (m, 1H, CONHC**H**CH); 4.18 (d, 1H, J = 3.3 Hz, C**H**OTIPS); 4.02 (m, 1H, CONHC**H**CH_2); 2.95–2.75 (m, 4H, C**H₂**Ar, SC**H₂**CH_3); 2.05 (m, 1H, NHCHC**H**Me_2); 1.92 (m, 1H, OCHC**H**Me_2); 1.20 (t, 3H, J = 7.5 Hz, SCH_2**CH₃**); 1.06 (m, 24H, TIPS, NHCHCH(Me)**Me**); 1.01–0.95 (m, 6H, OCHCH(**Me**)Me, NHCHCH(Me)**Me**); 0.88 (d, 3H, J = 6.3 Hz, OCHCH(**Me**)Me); ^{13}C NMR: (300 MHz, $CDCl_3$) δ 196.3, 195.9, 172.4, 170.9, 169.8, 158.6, 149.0, 136.4, 132.2, 131.2, 130.3, 128.5, 128.4, 128.3, 128.2, 127.9, 127.0, 125.0, 124.2, 118.0, 114.5, 111.4, 96.7, 78.0, 73.7, 70.8, 61.8, 59.2, 55.2, 39.2, 33.8, 29.9, 23.8, 19.1, 18.4, 18.1, 18.0, 17.7, 17.5, 14.1, 12.4; ^{19}F NMR: (75 MHz, $CDCl_3$) δ –70.0 (s, 3F, CF_3); HRMS (FAB+) exact mass calculated for [M+H] ($C_{50}H_{64}N_4O_9F_3SiS$) requires *m/z* 981.4115, found *m/z* 981.4107; $[\alpha]_D^{25} = -179.9$ (c = 0.30, $CHCl_3$).



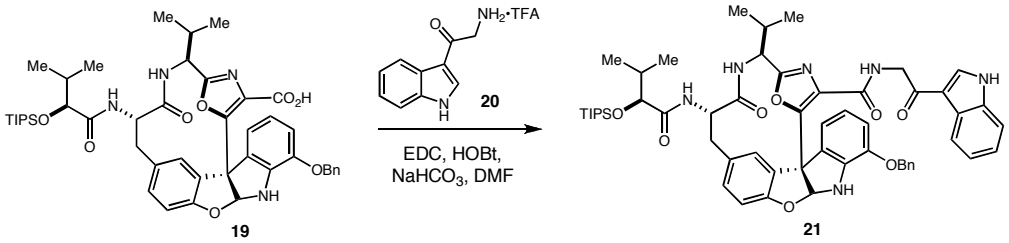
Oxazole 4: To a solution of **3** (125 mg, 0.127 mmol) in benzene (11 mL) was added DAST (1.1 mL) dropwise by syringe. The solution was stirred at room temperature for 3 hours before being diluted with EtOAc and a saturated solution of $NaHCO_3$. The layers were separated and the aqueous layer was washed with ethyl acetate 3 x 50 mL. The combined organics were washed with brine and concentrated. The resulting oil was

purified on silica gel (20% EtOAc in hexanes) to yield the title compound (99 mg, 81%) as a pale yellow solid. IR (film): 3405, 3286, 2926, 2868, 1739, 1656, 1494, 1463, 1291, 1251, 1201, 1157, 990, 879 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$): δ 7.63 (d, 1H, J = 1.5 Hz, Ar-**H**), 7.40–7.26 (m, 5H, Ar-**H**), 7.18–7.08 (m, 2H, Ar-**H**), 6.99–6.93 (m, 2H, Ar-**H**), 6.84 (s, 1H, OC**H**N), 6.78 (d, 1H, J = 8.4 Hz, Ar-**H**), 5.26–5.11 (m, 3H, OC**H**$_2$Ph, CONHC**H**CH), 4.71 (m, 1H, CONHC**H**CH_2), 3.96 (d, 1H, J = 3.0 Hz, C**H**OTIPS), 3.42 (t, 1H, J = 12.3 Hz, C**H**$_2$Ar), 2.99–2.75 (m, 2H, SC**H**$_2$$CH_3$), 2.64 (dd, 1H, J = 12.3, 3.3 Hz, C**H**$_2$Ar), 2.43 (m, 1H, NHCHC**H**$(CH_3)_2$), 1.72 (m, 1H, OCHC**H**$(CH_3)_2$), 1.18 (t, 3H, J = 7.5 Hz, SCH_2C**H**$_3$), 1.07 (m, 24H, TIPS and NHCHCH(**CH**$_3$)$_2$), 0.91–0.87 (m, 6H, NHCHCH(**CH**$_3$)$_2$, OCHCH(**Me**)Me), 0.63 (d, 3H, J = 7.2 Hz, OCHCH(**Me**)Me); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 186.2, 172.4, 171.7, 160.8, 156.8, 150.2, 149.7, 136.8, 136.2, 134.0, 130.4, 130.2, 129.4, 129.2, 128.8, 128.7, 128.6, 128.1, 127.6, 127.4, 115.0, 114.6, 110.7, 100.3, 77.9, 71.0, 60.9, 55.3, 53.5, 39.0, 34.0, 28.9, 23.0, 19.8, 18.3, 18.2, 18.0, 17.5, 17.0, 14.4, 12.6; HRMS: (FAB+) exact mass calculated for [M+H] ($C_{50}H_{62}F_3N_4O_8SiS$) requires *m/z* 963.4010, found *m/z* 963.3998; $[\alpha]_D^{25}$ = –61.01 (c = 0.55, $CHCl_3$).



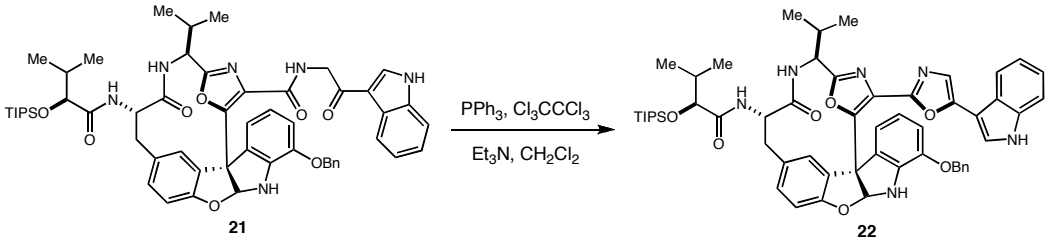
Acid 20: To a solution of **4** (84 mg, 0.087 mmol) in THF/MeOH/H_2O (4.4 mL, 10:2:1) was added LiOH•H_2O (36.5 mg, 0.87 mmol) with stirring. After the reaction was judged

complete by TLC analysis (2 hours), the reaction mixture was diluted with 50 mL of diethyl ether, acidified with 1N HCl to pH 2, and washed with 20 mL of brine. The organic portion was dried over sodium sulfate and concentrated *in vacuo*. These crude extracts were purified by column chromatography (50% EtOAc/Hexanes to 10% MeOH in CH_2Cl_2) to yield the title compound (71 mg, 99%) as a white amorphous solid. IR (Film): 3405, 2917, 2849, 1654, 1498, 1464, 1289, 1251, 1209, 1068, 882, 754, 684 cm^{-1}; ^1H NMR: (300 MHz, CD_3OD): δ 7.54–7.26 (m, 6H, Ar-**H**), 7.18 (dd, 1H, J = 8.2, 1.6 Hz, Ar-**H**), 6.94 (s, 1H, OC**H**N), 6.87–6.65 (m, 4H, Ar-**H**), 5.08 (s, 2H, OC**H**$_2$Ph), 4.93 (m, 1H, CONHC**H**CH), 4.53 (m, 1H, CONHC**H**CH_2), 4.16 (d, 1H, J = 3.9 Hz, C**H**OTIPS), 3.15 (t, 1H, J = 12.3 Hz, C**H**$_2$Ar), 2.85 (dd, 1H, J = 12.3, 3.8 Hz, C**H**$_2$Ar), 2.36 (m, 1H, NHCHC**H**$(CH_3)_2$), 2.05 (m, 1H, OCHC**H**$(CH_3)_2$), 1.09 (m, 24H, TIPS and NHCHCH(**C**$\mathbf{H_3}$)$_2$), 1.04–1.01 (m, 6H, NHCHCH(**C**$\mathbf{H_3}$)$_2$, OCHCH(**Me**)Me), 0.87 (d, 3H, J = 6.9 Hz, OCHCH(**Me**)Me); ^{13}C NMR: (75 MHz, CD_3OD) δ 172.7, 172.6, 165.9, 160.0, 157.2, 154.0, 144.0, 138.3, 137.0, 133.0, 130.6, 130.1, 130.0, 128.7, 128.2, 127.9, 127.6, 127.4, 127.3, 120.3, 114.9, 112.1, 110.2, 103.9, 70.2, 61.5, 55.6, 53.8, 38.6, 33.8, 28.6, 19.1, 17.6, 17.5, 17.1, 17.0, 16.6, 12.2; HRMS: (FAB+) exact mass calculated for [M+Na] ($C_{46}H_{58}N_4O_8SiNa$) requires *m/z* 845.3921, found *m/z* 845.3914; $[\alpha]_D^{25}$ = –100.66 (c = 0.493, $CHCl_3$).



Ketoindole 21: To a solution of **19** (36.4 mg, 0.044 mmol) in DMF (2.2 mL) was added **20** (24 mg, 0.088 mmol), EDC•HCl (10.2 mg, 0.052 mmol), HOBt (7.2 mg, 0.052 mmol), and $NaHCO_3$ (14.8 mg, 0.18 mmol). The solution was stirred at room temperature for 12 hours before being diluted with EtOAc and brine. The layers were separated and the aqueous was washed with ethyl acetate. The combined organics were washed with brine and concentrated. The resulting oil was purified on silica gel (40% EtOAc in hexanes) to yield the title compound (28 mg, 68%) as a pale white solid. IR (film): 3404, 3287, 2962, 2868, 1654, 1500, 1465, 1435, 1289, 1248, 1210, 1119, 1065, 913, 882, 843, 732, 685 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$): δ 9.13 (d, 1H, J = 2.4 Hz, C=CN**H**), 8.24 (m, 1H, Ar-**H**), 7.90 (t, 1H, J = 4.6 Hz, Ar-**H**), 7.73 (d, 1H, J = 3.3 Hz, Ar-**H**), 7.58 (d, 1H, J = 1.8 Hz, Ar-**H**), 7.28–7.22 (m, 9H, Ar-**H**), 7.08 (dd, 1H, J = 8.2, 1.6 Hz, Ar-**H**), 6.89 (t, 1H, J = 4.4 Hz, Ar-**H**), 6.70 (m, 2H, Ar-**H**, OC**H**N), 6.31 (br d, 1H, J = 8.4 Hz, CON**H**), 5.62, (s, 1H, CON**H**), 5.16 (dd, 1H, J = 9.0, 5.6, CONHC**H**CH), 4.87 (dd, 2H, J = 24.6, 11.4 Hz, OC$\mathbf{H}_2$Ph), 4.54 (t, 2H, J = 4.8 Hz, C$\mathbf{H_2}$CO), 4.46 (m, 1H, CONHC**H**CH_2), 4.13 (d, 1H, J = 3.3 Hz, C**H**OTIPS), 3.36 (t, 1H, J = 12.0 Hz, C$\mathbf{H}_2$Ar), 2.74 (dd, 1H, J = 12.0, 3.3 Hz, C$\mathbf{H}_2$Ar), 2.44 (m, 1H, NHCHC**H**$(CH_3)_2$), 1.97 (m, 1H, OCHC**H**$(CH_3)_2$), 1.09 (m, 24H, TIPS and NHCHCH(**C$\mathbf{H_3}$**)$_2$), 0.98–0.87 (m, 9H, NHCHCH(**C$\mathbf{H_3}$**)$_2$, OCHCH(**Me**)$_2$); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 188.4, 171.9, 160.8, 159.5, 157.2, 153.4, 144.0, 138.1, 136.8, 136.2, 131.4, 130.9, 130.6, 130.1, 129.6, 128.4, 128.2, 128.0, 127.8, 127.4, 125.1, 123.9, 122.9, 121.9, 120.6, 115.2, 115.1, 112.0, 111.7, 110.6, 103.7, 77.9, 77.2, 70.0,

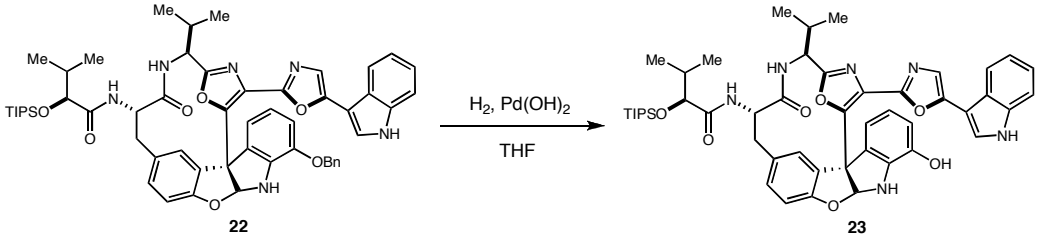
61.4, 56.0, 53.1, 45.9, 38.7, 33.9, 28.5, 19.6, 18.1, 18.0, 17.7, 17.5, 17.2, 12.4; HRMS: (FAB+) exact mass calculated for [M+H] ($C_{56}H_{67}N_6O_8Si$) requires *m/z* 979.4789, found *m/z* 979.4765; $[\alpha]_D^{25}$ = –42.44 (c = 0.147, $CHCl_3$).



21 22

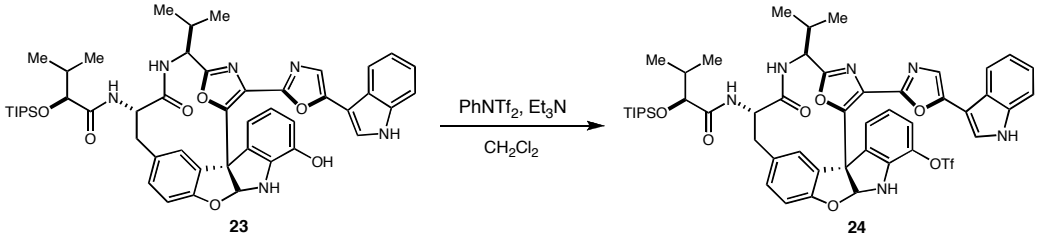
Bisoxazole 22: To a solution of PPh_3 (136 mg, 0.52 mmol) in CH_2Cl_2 (1.8 mL) was added C_2Cl_6 (123 mg, 0.52 mmol). The solution was stirred at room temperature for 10 minutes at which time Et_3N (0.144 mL, 1.04 mmol) was added dropwise. The resultant solution was stirred for 10 minutes at which time it was added dropwise via cannula to a stirred CH_2Cl_2 (2.8 mL) solution of **21** (51 mg, 0.052 mmol) at 0 °C and held at this temperature for 10 minutes, at which point it was allowed to warm to room temperature and stirred for an additional 10 minutes. The solution was then diluted with a saturated solution of $NaHCO_3$. The layers were separated and the aqueous was washed with CH_2Cl_2 3 x 5 mL. The combined organics were washed with brine and concentrated. The resulting oil was purified on silica gel (40% EtOAc in hexanes) to yield the title compound (47.7 mg, 95%) as a pale amorphous solid. IR (film): 3405, 3289, 2961, 2868, 1655, 1498, 1460, 1288, 1254, 1207, 1116, 1096, 1061, 917, 882, 738, 685 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$): δ 8.12 (s, 1H, C=CN**H**), 7.68–6.56 (m, 18H, Ar-**H**, OC**H**N), 5.41 (s, 1H, CON**H**), 5.06–4.86 (m, 3H, CONHC**H**CH, OC**H**$_2$Ph), 4.67 (m, 1H, CONHC**H**CH_2), 4.09 (d, 1H, J = 3.3 Hz, C**H**OTIPS), 3.34 (t, 1H, J = 12.0 Hz, C**H**$_2$Ar),

2.77 (dd, 1H, J = 12.0, 3.3 Hz, C**H**$_2$Ar), 2.38 (m, 1H, NHCHC**H**$(CH_3)_2$), 1.95 (m, 1H, OCHC**H**$(CH_3)_2$), 1.07 (m, 24H, TIPS and NHCHCH(**CH_3**$)_2$), 0.96 (d, 3H, J = 6.9 Hz, NHCHCH(**CH_3**$)_2$), 0.90 (d, 3H, J = 6.9 Hz, OCHCH(**Me**)Me), 0.84 (d, 3H, J = 6.9 Hz, OCHCH(**Me**)Me); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 172.1, 172.0, 161.8, 157.5, 152.5, 149.9, 148.3, 143.7, 137.9, 137.4, 136.3, 130.4, 130.1, 129.7, 129.2, 129.0, 128.8, 128.5, 128.1, 127.6, 124.0, 123.1, 122.9, 121.6, 121.2, 121.1, 119.8, 115.9, 112.4, 111.8, 110.9, 105.3, 103.3, 78.1, 70.2, 62.1, 55.8, 54.4, 39.0, 34.1, 29.5, 19.8, 18.3, 18.2, 17.6, 17.5, 12.5; HRMS: (FAB+) exact mass calculated for [M+H] ($C_{56}H_{65}N_6O_7Si$) requires *m/z* 961.4687, found *m/z* 961.4682; $[\alpha]_D^{25} = -115.47$ (c = 0.187, $CHCl_3$).



Phenol 23: To a solution of **22** (47.5 mg, 0.049 mmol) in THF (5 mL) was added $Pd(OH)_2/C$ (120 mg). The solution was sparged with H_2 for 20 minutes and kept under a H_2 atmosphere for 7 hours. At this time the solution was filtered through a silica plug, concentrated, and the resulting oil was purified on silica gel (40%–60% EtOAc in hexanes) to yield the title compound (38.0 mg, 88%) as a pale amorphous solid. IR (film): 3287, 2962, 2868, 1652, 1496, 1458, 1292, 1254, 1191, 1099, 1061, 917, 882, 738, 683 cm^{-1}; ^{1}H NMR: (300 MHz, CD_3OD): δ 8.67 (d, 1H, J = 7.2 Hz, C=CN**H**), 7.64 (m, 1H, Ar-**H**), 7.49–7.41 (m, 3H, Ar-**H**), 7.21–7.13 (m, 4H, Ar-**H)**, 7.04 (d, 1H, J = 1.8 Hz, Ar-**H**), 6.84–6.80 (m, 2H, Ar-**H**), 6.57 (dd, 1H, J = 6.0, 2.7 Hz, Ar-**H**), 6.39 (m, 2H,

Ar-**H**, OC**H**N), 4.69 (t, 1H, J = 7.2 Hz, CONHC**H**CH), 4.55 (m, 1H, CONHC**H**CH_2), 4.15 (d, 1H, J = 3.9 Hz, C**H**OTIPS), 3.06 (t, 1H, J = 12.0 Hz, C**H**$_2$Ar), 2.85 (dd, 1H, J = 12.0, 4.0 Hz, C**H**$_2$Ar), 2.17–2.00 (m, 2H, NHCHC**H**$(CH_3)_2$, OCHC**H**$(CH_3)_2$), 1.10–0.96 (m, 33H, TIPS, NHCHCH(**C**$\mathbf{H_3}$)$_2$, OCHCH(**Me**)$_2$); ^{13}C NMR: (75 MHz, CD_3OD) δ 172.8, 172.3, 162.6, 157.6, 151.7, 151.2, 149.6, 142.0, 137.0, 136.7, 131.2, 129.7, 129.0, 128.9, 128.4, 127.8, 123.7, 123.6, 121.9, 120.3, 120.0, 119.2, 118.8, 115.0, 113.4, 111.4, 110.1, 103.7, 103.2, 78.1, 61.9, 55.6, 55.5, 38.1, 33.8, 29.8, 18.4, 18.0, 17.2, 17.1, 16.7, 12.2; HRMS: (FAB+) exact mass calculated for [M+H] ($C_{49}H_{58}N_6O_7Si$) requires *m/z* 870.4136, found *m/z* 870.4132; $[\alpha]_D^{25} = -102.52$ (c = 0.173, $CHCl_3$).

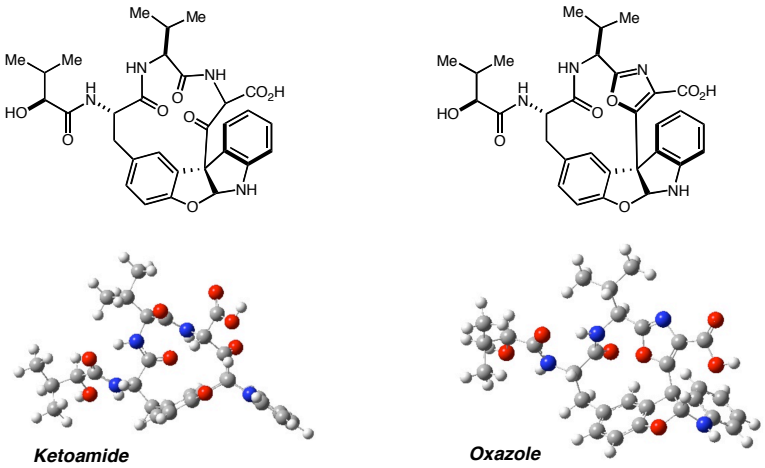


Triflate 24: To a solution of **23** (38 mg, 0.044 mmol) in CH_2Cl_2 (4.3 mL) was added $PhNTf_2$ (39 mg, 0.109 mmol) and Et_3N (30.4 μL, 0.218 mmol). The solution was stirred under argon for 30 minutes and then diluted with brine. The aqueous layer was washed with EtOAc, and the combined organics were dried over Na_2SO_4. After concentration of the solvents *in vacuo*, the resulting oil was purified on silica gel (30% EtOAc in hexanes) to yield the title compound (30 mg, 67%) as a pale yellow-orange amorphous solid. IR (film): 3287, 2962, 2869, 1652, 1496, 1471, 1424, 1213, 1139, 1062, 916, 882, 812, 742, 668 cm^{-1}; ^{1}H NMR: (300 MHz, CD_3OD): δ 7.68 (m, 1H, Ar-**H**), 7.48–7.42 (m, 2H, Ar-**H**), 7.26–7.02 (m, 7H, Ar-**H)**, 6.85 (m, 2H, Ar-**H**, OC**H**N), 6.52 (dd, 1H, J = 7.5, 6.6 Hz,

Ar-**H**), 4.69 (d, 1H, J = 7.2 Hz, CONHC**H**CH), 4.56 (dd, 1H, J = 14.2, 3.9 Hz, CONHC**H**CH_2), 4.16 (d, 1H, J = 3.9 Hz, C**H**OTIPS), 3.07 (t, 1H, J = 12.0 Hz, C**H**$_2$Ar), 2.87 (dd, 1H, J = 12.0, 3.9 Hz, C**H**$_2$Ar), 2.19–2.00 (m, 2H, NHCHC**H**$(CH_3)_2$, OCHC**H**$(CH_3)_2$), 1.12–0.99 (m, 33H, TIPS, NHCHCH(**CH$_3$**)$_2$, OCHCH(**Me**)$_2$); ^{13}C NMR: (75 MHz, CD_3OD) δ 172.7, 172.2, 162.8, 157.7, 151.4, 150.0, 149.5, 141.5, 136.8, 133.3, 131.8, 130.3, 129.9, 129.1, 128.8, 128.1, 123.7, 123.0, 122.2, 122.1, 121.2, 120.7, 120.1, 119.7, 119.2, 118.8, 116.5, 111.5, 110.4, 103.3, 103.2, 78.1, 61.2, 55.4, 38.0, 33.8, 29.8, 18.4, 18.0, 17.2, 17.1, 16.7, 12.2; ^{19}F NMR: (75 MHz, CD_3OD) δ –75.6 (s, 3F, CF_3); HRMS: (FAB+) exact mass calculated for [M+H] ($C_{50}H_{58}N_6O_9F_3SiS$) requires *m/z* 1003.371, found *m/z* 1003.369; $[\alpha]_D^{25}$ = –119.34 (c = 0.126 $CHCl_3$).

DFT calculation of ring strain: Both structures shown below were minimized using the B3LYP density functional and the 3-21G level of theory in the Gaussian 03 suite of programs.

Table 1: Ring contraction thermochemistry



Ketoamide ***Oxazole***

Entry	E (hartree)	ΔE° (hartree)	ΔE° (kcal)
Ketoamide	–1973.637342		
Oxazole	–1897.607806		
Water	–75.97396515		
		-0.07557138	-47.42

Coordinates, Level of Calculation, and Energies:

Keto-amide

E (B3LYP/3-21G) = –1973.65734238 a.u.

0 1

C	2.16701900	-1.14812500	0.56846500
C	1.10324700	-1.59966100	-0.19277000
C	0.01293600	-2.21308900	0.44484300
C	0.05850600	-2.40007100	1.83527500
C	1.13290900	-1.94096600	2.60587900

C	2.17067900	-1.27926300	1.95724300
O	3.23845400	-0.64856400	2.57808000
C	4.40269800	-1.21050700	-0.63712300
C	-0.28336200	2.63891600	0.17571500
O	-0.09304400	3.27418400	1.22576600
C	-1.26500000	-2.48914200	-0.33561200
C	-2.23942600	-1.31395000	-0.11964100
C	-1.66756800	-0.01089700	-0.73659300
O	-0.84014300	-0.00747800	-1.68199800
C	5.51692600	-1.43450600	0.19288900
C	-1.66877200	2.46241400	-0.49649300
C	-2.66777400	3.52471600	-0.00358300
C	-4.09035700	3.25702800	-0.54505400
C	-2.18122200	4.92916300	-0.42509500
N	-2.13397800	1.10225800	-0.13101100
N	-3.57557400	-1.59355400	-0.67647100
C	-4.65732500	-0.91612000	-0.24612600
C	-5.97458000	-1.38794200	-0.87303000
C	-7.00954900	-1.79382700	0.20430300
C	-6.39109900	-2.83421400	1.15912400
O	-4.60481600	0.01355900	0.60438000
O	-5.62292200	-2.53374900	-1.71721800
C	4.11675800	-0.05733200	1.50019100
N	5.37268500	-0.73989700	1.39130900
C	3.39587500	-0.36141100	0.11384000
C	4.35079000	-1.74126500	-1.91425400
C	5.41876000	-2.53310200	-2.36557400
C	6.51299500	-2.77148500	-1.53215200
C	6.57918600	-2.22273900	-0.24484100
C	2.75788900	3.19029700	0.08719700
H	1.05979300	-1.41024600	-1.25656100
H	-0.77449000	-2.88567600	2.33379700
H	1.14840500	-2.06006400	3.68042900
H	-2.91940900	0.99128500	0.51872000
H	-3.74043500	-2.31483000	-1.37799900
H	6.08363600	-0.68314600	2.10717200
H	-1.04702200	-2.57024100	-1.40489800
H	-1.74450000	-3.41258700	0.00771300
H	-1.55699400	2.50642800	-1.58551800
H	-2.66559400	3.47913900	1.09253800
H	-4.76904100	4.04163300	-0.19219200
H	-4.08427800	3.28124700	-1.64233300
H	-4.48503200	2.29053200	-0.21766300
H	-2.89018900	5.68930200	-0.07943800
H	-1.20391000	5.13410600	0.01777300
H	-2.10899300	4.99740800	-1.51772300

H	-6.37665700	-0.55707500	-1.47157600
H	-7.84171500	-2.26855600	-0.33910700
H	-5.63825500	-2.35407600	1.79380000
H	-7.15920300	-3.27225100	1.80434200
H	-5.91611000	-3.62859200	0.57491600
H	3.51222900	-1.52030900	-2.55996900
H	5.39460600	-2.95221600	-3.36378800
H	7.33354800	-3.38589600	-1.88502600
H	-2.36967000	-1.14138300	0.95280800
H	4.20824600	1.00004500	1.73837500
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H	-8.25530300	-0.86929200	1.73215500
H	-6.71870200	-0.01472600	1.39713900
H	-8.07933800	0.11295600	0.26288300
H	-6.43878300	-2.83904600	-2.19113500
O	2.43319400	4.23182500	-0.44392500
C	2.02112900	1.85735600	0.14619300
H	1.94766800	1.55808500	1.19526700
N	0.71139700	1.96115200	-0.47111900
H	0.47198300	1.35816100	-1.26404900
O	3.96685900	3.01434100	0.76016200
H	4.48649400	3.86422700	0.72475800
H	7.43870400	-2.40480800	0.38873600
C	2.85795900	0.83528000	-0.66103300
O	2.96133400	0.93993000	-1.88095600

Oxazole

E (B3LYP/3-21G) = –1897.60780585 a.u.

0 1

C	-1.76559700	-1.63418300	-0.37382300
C	-0.72066600	-1.79744100	0.51976400
C	0.35952200	-2.62542300	0.17721000
C	0.29096900	-3.37196100	-1.01018900
C	-0.80242200	-3.26904500	-1.87782400
C	-1.80458800	-2.35511700	-1.56359300
O	-2.85932700	-2.00127100	-2.40144700
C	-3.88472500	-0.75972300	0.73350500
C	1.67009000	-2.47481300	0.94363900
C	2.35802200	-1.17459200	0.45669300
C	1.63137000	0.06606700	1.05143800
O	1.04032900	0.04498900	2.14731000
C	-5.04065800	-1.34157900	0.18113600
C	0.93042300	2.37775100	0.53583900
C	1.60948800	3.63575300	-0.06276900

C	3.09649700	3.69521200	0.35944800
C	0.86962900	4.91400800	0.39280500
N	1.69629000	1.15753900	0.23961100
N	3.78585300	-1.11847600	0.82381300
C	4.62032900	-0.26836700	0.19477600
C	6.07674100	-0.36694300	0.66164600
C	7.02702100	-0.73595100	-0.50402700
C	6.54402700	-2.03227400	-1.18405800
O	4.25490700	0.53100500	-0.70948100
O	6.09620400	-1.40406000	1.69688100
C	-3.66268300	-0.95413600	-1.69937200
N	-4.90811500	-1.47472800	-1.19347000
C	-2.85728600	-0.56139400	-0.37770800
C	-3.78254900	-0.51330100	2.08938500
C	-4.86142400	-0.84888000	2.92434600
C	-6.00764800	-1.42923400	2.37847000
C	-6.11265700	-1.68393100	1.00453800
C	-3.83487100	2.67583200	-1.03559400
H	-0.65544100	-1.20086300	1.41646500
H	1.11770700	-4.02133200	-1.27960700
H	-0.84822600	-3.83425600	-2.79867300
H	2.36796200	1.13594800	-0.53137100
H	4.18959900	-1.69188100	1.56332900
H	-5.64638800	-1.78933500	-1.80780000
H	1.49258200	-2.38059000	2.01978900
H	2.33309000	-3.32464300	0.74950600
H	0.88108300	2.46599800	1.62980500
H	1.54661400	3.55936200	-1.15634100
H	3.55344900	4.60193500	-0.05194700
H	3.17051900	3.74269800	1.45328100
H	3.66280900	2.82802200	0.00753500
H	1.33836600	5.79439000	-0.05980800
H	-0.18172400	4.87512300	0.09898200
H	0.93534000	5.01331000	1.48370900
H	6.36366000	0.61351000	1.06882800
H	8.00948900	-0.92792800	-0.04411500
H	5.63008500	-1.83755000	-1.75621500
H	7.30555400	-2.41688300	-1.86994100
H	6.33307200	-2.78714600	-0.42023900
H	-2.88607300	-0.06331000	2.50089700
H	-4.80129700	-0.65739400	3.98834300
H	-6.83746100	-1.68924500	3.02590000
H	2.30290000	-1.11690500	-0.63334700
H	-3.78471700	-0.14556800	-2.41268800
C	7.17196600	0.43316800	-1.49916800
H	7.81330700	0.13923700	-2.33668300

H	6.18441800	0.71594000	-1.86776200
H	7.62224500	1.30610000	-1.01071800
H	7.02297300	-1.49092200	2.03911300
O	-4.13024100	3.85391600	-1.17403000
O	-4.74327100	1.64472000	-1.26630400
H	-5.62631400	2.04969800	-1.48466800
H	-7.00869200	-2.13502500	0.59570300
C	-2.56109600	2.11223400	-0.61910500
C	-2.22167600	0.80385500	-0.38233200
C	-0.48471600	2.16734100	0.02896900
O	-0.89460700	0.82328300	0.03410800
N	-1.44794600	2.95441800	-0.35564400

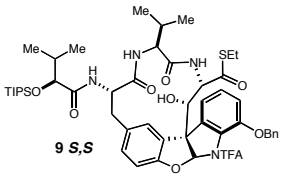
Water
E (B3LYP/3-21G) = –75.97396515 a.u.

0 1

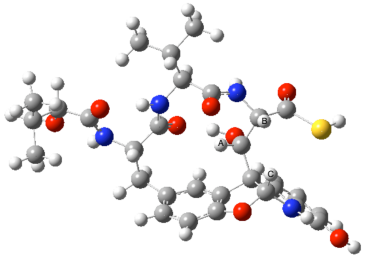
O	0.00000000	0.00000000	0.12275500
H	0.00000000	0.78546200	-0.49102000
H	0.00000000	-0.78546200	-0.49102000

Stereochemistry of magnesium aldol product: Each of the four possible aldol diastereomers was minimized using the B3LYP density functional and the 3-21G level of theory in the Gaussian 03 suite of programs. These four minimized structures are shown below, along with the dihedral angles between the alcohol and amine methines, and the likelihood of producing the observed NOESY crosspeaks.

Stereochemistry of aldol product by DFT calculations (B3LYP 3-21G)



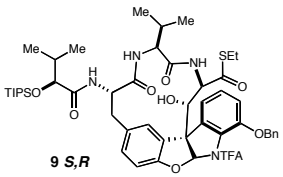
9 *S,S*



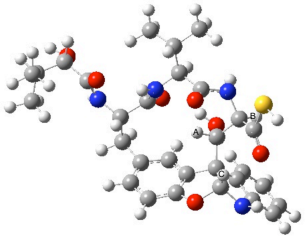
A-B dihedral = 60.7 °

Likely NOE A-C

Likely NOE B-C



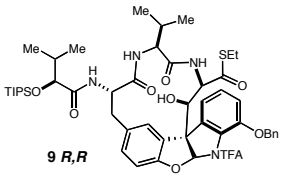
9 *S,R*



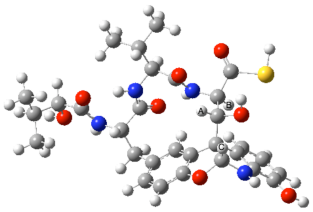
A-B dihedral = 171.7 °

Likely NOE A-C

Unlikely NOE B-C



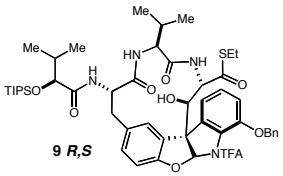
9 *R,R*



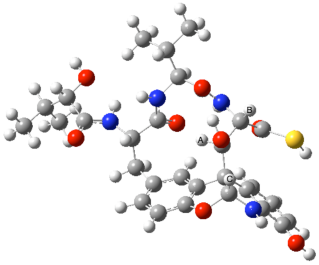
A-B dihedral = 159.4 °

Likely NOE A-C

Unlikely NOE B-C



9 *R,S*



A-B dihedral = 124.3 °

Unlikely NOE A-C

Likely NOE B-C

Coordinates, Level of Calculation, and Energies:

9 (*S*, *S*)
E (B3LYP/3-21G) = –2371.04216078 a.u.

0 1

C	-1.61007600	-1.78996300	-0.35573700
C	-0.57843600	-2.00599500	0.54723900
C	0.58945700	-2.65740300	0.12953700
C	0.62237800	-3.23209500	-1.15264700
C	-0.44237300	-3.07720000	-2.04597000
C	-1.52202500	-2.28525200	-1.65453100
O	-2.49899800	-1.80228400	-2.51201800
C	-3.83393500	-0.92758000	0.61880700
C	0.34794900	2.45700300	-0.71839000
O	0.31019200	2.10226900	-1.90804400
C	1.86731000	-2.46125200	0.93459300
C	2.62708900	-1.22154800	0.39099300
C	1.90275800	0.11558600	0.72368100
O	1.05568500	0.21248300	1.64974100
C	-4.93053700	-1.24853600	-0.18574000
C	1.68917100	2.50475600	0.05637800
C	2.61907700	3.54841700	-0.60230900
C	4.05493900	3.49369300	-0.03692500
C	2.01631500	4.95742900	-0.40480700
N	2.27984300	1.14866900	-0.05627800
N	4.00428100	-1.17596000	0.92426600
C	4.97986900	-0.48800900	0.30323900
C	6.36189500	-0.65436700	0.94150500
C	7.36137900	-1.31856400	-0.03933100
C	6.79404500	-2.66179300	-0.54009700
O	4.79456900	0.22086100	-0.72436300
O	6.15603400	-1.49165800	2.12548700
C	-3.27733500	-0.74344600	-1.76083200
N	-4.63673500	-1.11849900	-1.53645800
C	-2.64616400	-0.65463200	-0.29489400
C	-3.94301200	-0.94931600	2.00583500
C	-5.17213800	-1.30481400	2.57261300
C	-6.26520400	-1.63285000	1.76072500
C	-6.15801700	-1.60420700	0.37081500
C	-3.16493900	2.66109200	0.40785100
O	-7.18622400	-1.88968100	-0.52981600
H	-0.61289000	-1.53461700	1.51472100
H	1.51197200	-3.76127100	-1.48037600

H	-0.39744200	-3.47588400	-3.05037500
H	3.06210900	0.98750000	-0.70345100
H	4.27591600	-1.68107800	1.76797200
H	-5.34047000	-1.18162300	-2.25845800
H	1.63801300	-2.29456800	1.99170500
H	2.53319200	-3.32694800	0.84134900
H	1.53185600	2.72957400	1.11528600
H	2.62914800	3.31063700	-1.67404400
H	4.66059500	4.27983900	-0.50185200
H	4.04010400	3.67076200	1.04598300
H	4.53511400	2.53120100	-0.23339900
H	2.60779800	5.70019000	-0.94959500
H	0.98324500	5.00635400	-0.76548200
H	2.02548600	5.22487800	0.65925700
H	6.72780800	0.34586800	1.21351500
H	8.27107900	-1.52119600	0.54821700
H	5.96281900	-2.48609400	-1.23211800
H	7.56462400	-3.23353100	-1.06664400
H	6.43139800	-3.24701500	0.31057000
H	-3.10056200	-0.64948900	2.60803400
H	-5.28555800	-1.32057400	3.64969100
H	-7.21160500	-1.90622500	2.21776000
H	2.70375200	-1.29145900	-0.69835200
H	-3.16264900	0.15215000	-2.37375500
C	7.72886700	-0.36710200	-1.19564200
H	8.40155000	-0.87058200	-1.89767000
H	6.81966500	-0.05492900	-1.71252200
H	8.23532900	0.52879900	-0.81655400
H	7.03716300	-1.67523600	2.54184000
H	-8.00488100	-2.14376600	-0.03267900
O	-3.05068600	3.20047500	1.49174700
C	-2.04481100	2.06022800	-0.39802900
H	-2.18545000	2.16292200	-1.47285600
O	-1.52570800	0.59724000	1.45407100
H	-0.52659400	0.53619500	1.62452700
C	-1.75087200	0.57669500	0.02075700
H	-0.82629300	0.37691000	-0.53065800
S	-4.81530000	2.46946500	-0.49571800
H	-5.56718100	2.87254300	0.57889400
N	-0.78431400	2.73257200	0.00754500
H	-0.73953700	2.88934800	1.01293200

9 (*S*, *R*)
E (B3LYP/3-21G) = –2371.04543883 a.u.

0 1

C	-1.80650900	-1.82928500	-0.39265900
C	-0.74068000	-2.17967000	0.42408100
C	0.38807100	-2.80548800	-0.12252900
C	0.34352600	-3.23100600	-1.46034900
C	-0.76533600	-2.96320700	-2.26882500
C	-1.80424900	-2.19639200	-1.73836300
O	-2.82029000	-1.62771300	-2.48203800
C	-3.98012400	-1.02136700	0.76343000
C	0.21500000	2.44837900	0.02011800
O	0.09328000	2.39064900	-1.21428000
C	1.70436800	-2.73802800	0.64142600
C	2.45626200	-1.43130400	0.26680200
C	1.78470700	-0.16390400	0.86946900
O	0.98942100	-0.21738100	1.84531000
C	-5.12241900	-1.18622500	-0.02776700
C	1.59739200	2.30724600	0.69334400
C	2.51389100	3.44961000	0.19825700
C	3.97199600	3.26832000	0.67241000
C	1.94648100	4.80260200	0.68361300
N	2.14022100	0.99157500	0.27180100
N	3.86115000	-1.49310200	0.72285700
C	4.81767000	-0.71232100	0.18878800
C	6.22506600	-1.00319400	0.71917700
C	7.18867100	-1.42160200	-0.41905600
C	6.60049500	-2.61635400	-1.19583400
O	4.59503200	0.17804900	-0.67765800
O	6.06632100	-2.08411000	1.69493400
C	-3.49944900	-0.59164600	-1.60465100
N	-4.87379300	-0.90593600	-1.36150100
C	-2.81233000	-0.68325600	-0.16152900
C	-4.04351600	-1.22024000	2.14052700
C	-5.26804500	-1.58583900	2.70982100
C	-6.40654800	-1.75199400	1.91059300
C	-6.34708900	-1.55099400	0.53318400
O	-7.41913500	-1.67128500	-0.35367900
H	-0.72050100	-1.84679300	1.44602200
H	1.20187200	-3.73624700	-1.89253300
H	-0.78709400	-3.25537900	-3.30999900
H	2.89122900	0.94865700	-0.43005800
H	4.16744900	-2.15717900	1.43438500
H	-5.59925800	-0.88092000	-2.06387200
H	1.52844500	-2.73930200	1.72179600
H	2.35488300	-3.58088800	0.38073600
H	1.51187900	2.31403400	1.78377700
H	2.47012300	3.41976900	-0.89810400

H	4.57284000	4.12039500	0.33540200
H	4.01176600	3.23631300	1.76868800
H	4.42022300	2.35459200	0.27252400
H	2.55223800	5.62432000	0.28812100
H	0.91277400	4.94938400	0.35199400
H	1.97580600	4.85321000	1.77936700
H	6.59958700	-0.08438900	1.19320200
H	8.11600000	-1.74990100	0.07691900
H	5.74840700	-2.28820200	-1.80151100
H	7.35102100	-3.04922100	-1.86468800
H	6.26434700	-3.38275700	-0.49042900
H	-3.16406800	-1.05170300	2.74010800
H	-5.34225800	-1.73800100	3.77971600
H	-7.34915800	-2.03566800	2.36915100
H	2.46897200	-1.31556300	-0.82131100
H	-3.34366600	0.35187900	-2.11656900
C	7.52248700	-0.22845800	-1.33702800
H	8.17515500	-0.55304200	-2.15396000
H	6.59834600	0.18604800	-1.74337700
H	8.03895000	0.56058900	-0.77683500
H	6.96047600	-2.32774300	2.04764500
H	-8.23266100	-1.94636900	0.14071600
C	-2.15860600	2.01496000	0.30940500
O	-1.58495100	0.22279500	1.70282000
H	-0.58583600	0.09245400	1.82344700
C	-1.87322100	0.48290800	0.28302100
H	-0.97895100	0.37955800	-0.33786400
N	-0.88177000	2.56842600	0.84931900
H	-0.76464100	2.39983200	1.84498400
H	-2.95266300	2.22825200	1.02992500
C	-2.47490200	2.74766300	-0.98265500
S	-2.31201300	4.63675800	-0.69774800
H	-2.86276900	4.92446600	-1.92344200
O	-2.91668500	2.30914200	-2.02725500

9 (*R*, *R*)
E (B3LYP/3-21G) = –2371.05397902 a.u.

0 1

C	-1.48884800	-1.54070300	-0.60074000
C	-0.44140400	-1.58377700	0.30434900
C	0.62090200	-2.48839800	0.11764000
C	0.57551900	-3.37200400	-0.96876500
C	-0.50225700	-3.37367000	-1.85911200
C	-1.52492100	-2.45157300	-1.66530200

O	-2.64058600	-2.34275400	-2.47593500
C	-3.70545900	-1.04817200	0.51163800
C	0.14923100	2.26840800	-0.39261200
O	-0.25689500	2.62509500	-1.51288900
C	1.86909400	-2.38651600	0.98948500
C	2.72102200	-1.21084500	0.47189900
C	2.03836600	0.12679100	0.84070300
O	1.32026300	0.26956300	1.86657500
C	-4.84530800	-1.63093700	-0.04889600
C	1.62124200	2.43005100	0.07006300
C	2.34361700	3.49132800	-0.77767500
C	3.85574000	3.54068800	-0.46172800
C	1.69721800	4.87155100	-0.51237600
N	2.26263200	1.10423100	-0.05836800
N	4.10315500	-1.21019000	0.98406000
C	5.05823700	-0.51219400	0.33603600
C	6.45475100	-0.64979800	0.94844900
C	7.44568600	-1.30926900	-0.04374400
C	6.88986400	-2.66676600	-0.51800400
O	4.83727800	0.17461000	-0.69764500
O	6.28672200	-1.47677600	2.14599400
C	-3.50408700	-1.24263800	-1.91639000
N	-4.75719900	-1.72203000	-1.42617100
C	-2.74366600	-0.67688200	-0.62157900
C	-3.57583200	-0.95129200	1.89527300
C	-4.63173000	-1.38436800	2.70611300
C	-5.78805600	-1.92495600	2.13258200
C	-5.90398800	-2.06466400	0.75079800
O	-6.99588600	-2.61150700	0.07920800
H	-0.39958200	-0.91468800	1.14782000
H	1.39006500	-4.07251000	-1.12226200
H	-0.55144500	-4.06757100	-2.68711200
H	2.99342000	0.94429600	-0.75736900
H	4.38467000	-1.69598100	1.83443300
H	-5.53115900	-2.01114900	-2.00745000
H	1.60555900	-2.18951600	2.03358000
H	2.45391900	-3.31002800	0.92643600
H	1.63238400	2.71252500	1.12839200
H	2.17941400	3.22809100	-1.82922900
H	4.33654500	4.29464600	-1.09494400
H	4.00592200	3.83274600	0.58562700
H	4.35786700	2.58209000	-0.62690300
H	2.12995500	5.62340800	-1.18087900
H	0.61767300	4.83043000	-0.67692900
H	1.88723500	5.18148200	0.52287900
H	6.81026600	0.35921500	1.20160200

H	8.37031700	-1.49075600	0.52720600
H	6.04174900	-2.51127000	-1.19411000
H	7.65844600	-3.23262200	-1.05392000
H	6.55362500	-3.24690500	0.34684600
H	-2.66542100	-0.58152100	2.35124100
H	-4.55352200	-1.30998800	3.78345100
H	-6.59944100	-2.25602200	2.77326400
H	2.78853600	-1.26542000	-0.61773200
H	-3.60516700	-0.51560400	-2.71675400
C	7.77283300	-0.36461400	-1.21769400
H	8.43519900	-0.86535200	-1.93148800
H	6.84623300	-0.07017700	-1.71367500
H	8.27543800	0.54192500	-0.85920100
H	7.17863400	-1.62820300	2.55242300
H	-7.69357500	-2.87895300	0.73010300
C	-2.10407600	1.68272100	0.39548800
C	-2.58105300	0.85816500	-0.84676300
N	-0.65440700	1.68307000	0.55099300
H	-0.19794600	1.31387900	1.39137100
H	-2.56394800	1.24226500	1.28390700
C	-2.55144900	3.16755000	0.40777100
S	-4.43950800	3.41951100	0.45504500
H	-4.29224300	4.73990800	0.82221100
O	-1.80528000	4.12339800	0.49941700
O	-3.93457600	1.26406200	-1.23959000
H	-3.87913200	2.12030200	-1.74194500
H	-1.86307600	1.04447200	-1.64773100

9 (*R*, *S*)
E (B3LYP/3-21G) = –2371.02441932 a.u.

0 1

C	-1.56354300	-1.62916100	-0.52990700
C	-0.47442400	-1.59661300	0.31746000
C	0.60504300	-2.47093700	0.10525300
C	0.49262000	-3.42626500	-0.91697600
C	-0.64382900	-3.50026500	-1.73779900
C	-1.66343700	-2.56756500	-1.55259400
O	-2.78596000	-2.39875400	-2.34993400
C	-3.65842300	-0.76362800	0.51165400
C	0.22718700	2.79012300	-0.64473000
O	-0.04166900	2.92661300	-1.86650500
C	1.91946900	-2.18543300	0.82218300
C	2.56300200	-0.93938100	0.17179900
C	1.86275600	0.38108200	0.54409300

O	1.16925200	0.56520200	1.56701800
C	-4.85539600	-1.24644800	-0.02804600
C	1.67281500	2.77327100	-0.11828600
C	2.60511400	3.74145600	-0.86719800
C	4.03134900	3.68045300	-0.26741600
C	2.04962400	5.18002500	-0.81414200
N	2.14214300	1.38740600	-0.33202900
N	3.98065800	-0.71266600	0.52798300
C	4.97136700	-1.17393200	-0.28409200
C	6.32915200	-0.52392500	0.00674700
C	7.27628700	-1.48828800	0.76614500
C	6.64788100	-1.92188800	2.10458500
O	4.79646700	-2.02508600	-1.17496300
O	6.04231700	0.68589600	0.79174700
C	-3.47773100	-1.11793100	-1.90328400
N	-4.79821900	-1.35480800	-1.40536700
C	-2.66232500	-0.58730900	-0.64177300
C	-3.49160100	-0.69495000	1.89231300
C	-4.56749000	-1.02029600	2.71985200
C	-5.78581700	-1.44515100	2.16871500
C	-5.93862300	-1.57660400	0.79164100
C	-2.95339700	2.16119900	1.07798700
O	-7.08386400	-2.02629600	0.13531700
H	-0.39278200	-0.84665400	1.09285200
H	1.31589900	-4.10875200	-1.10139200
H	-0.70908000	-4.23051900	-2.53297400
H	2.64951100	1.19324000	-1.19009500
H	4.24505800	0.03157700	1.17088900
H	-5.57142700	-1.69234200	-1.96134900
H	1.77150900	-1.99968900	1.89063400
H	2.62471800	-3.01087800	0.68485700
H	1.68751300	2.96624800	0.95737600
H	2.61801300	3.42302000	-1.91811000
H	4.71631600	4.27870200	-0.87812700
H	4.01912500	4.10885300	0.74292600
H	4.42825500	2.66069900	-0.19546800
H	2.73744700	5.86644600	-1.31901200
H	1.08020800	5.22860600	-1.31783400
H	1.93682400	5.51203200	0.22528300
H	6.77882100	-0.27339400	-0.96319900
H	8.19565800	-0.91977900	0.98077900
H	5.77008600	-2.55330800	1.93214200
H	7.37135600	-2.48749500	2.70058600
H	6.33343700	-1.04098100	2.67279700
H	-2.54940800	-0.37951100	2.31712000
H	-4.46555100	-0.95586700	3.79599100

H	-6.60936300	-1.69904500	2.82879100
H	2.54159700	-1.09235400	-0.91300500
H	-3.41951700	-0.44562200	-2.75068500
C	7.64119100	-2.69044900	-0.12971400
H	8.22929800	-3.41933600	0.43721100
H	6.72964500	-3.16342600	-0.50339200
H	8.23234900	-2.36572500	-0.99385800
H	6.90299800	1.05928800	1.11714700
H	-7.76952800	-2.29609800	0.79809200
O	-2.55354900	2.04524900	2.22619400
C	-2.07276000	2.14644800	-0.14222600
H	-2.44306800	2.87153400	-0.86957500
C	-1.92167400	0.77978500	-0.97086300
S	-4.73880600	2.43921800	0.59253400
H	-5.25025500	1.97744300	1.77717300
N	-0.71395000	2.51851000	0.29167800
H	-0.44589400	2.22182600	1.23145200
H	-0.87310700	0.54223600	-0.78650500
O	-2.10340400	1.09824200	-2.37422500
H	-1.37321500	1.76937800	-2.56139600

Crystal Structure Analysis for Intermediate 19 (k08308)

Contents

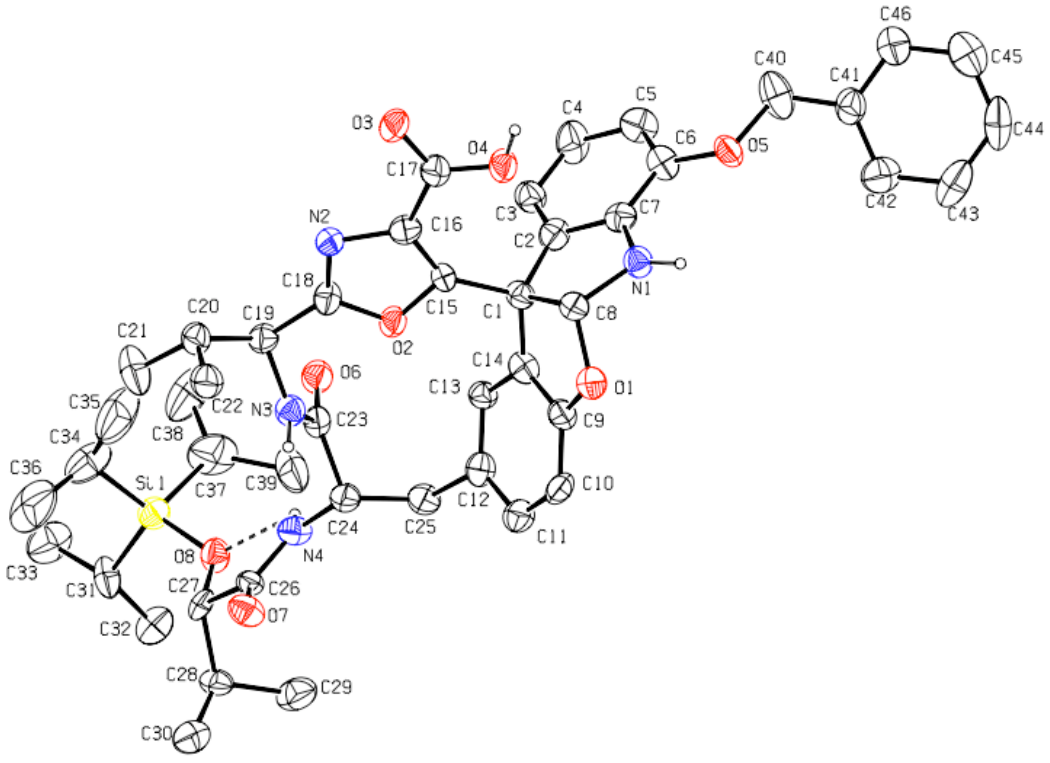


Table 1. Crystal data and structure refinement for k08308.

Identification code	k08308	
Empirical formula	C47 H59 Cl3 N4 O8 Si	
Formula weight	942.42	
Temperature	200(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C 2	
Unit cell dimensions	a = 19.546(4) Å	a= 90°.
	b = 17.360(4) Å	b= 105.63(3)°.
	c = 19.889(4) Å	g = 90°.
Volume	6499(2) $Å^3$	
Z	4	
Density (calculated)	0.963 Mg/m^3	
Absorption coefficient	0.201 mm^{-1}	
F(000)	1992	
Crystal size	0.40 x 0.30 x 0.20 mm^3	
Theta range for data collection	2.58 to 24.38°.	
Index ranges	-22<=h<=21, -19<=k<=20, 0<=l<=22	
Reflections collected	8612	
Independent reflections	5228 [R(int) = 0.0623]	
Completeness to theta = 24.38°	94.3 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.958 and 0.516	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5228 / 22 / 568	
Goodness-of-fit on F^2	1.111	
Final R indices [I>2sigma(I)]	R1 = 0.1136, wR2 = 0.2908	
R indices (all data)	R1 = 0.1515, wR2 = 0.3174	
Largest diff. peak and hole	0.532 and -0.316 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for k08308. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Si(1)	1845(2)	3815(2)	3117(2)	86(1)
O(1)	5341(4)	6479(4)	8038(3)	84(2)
O(2)	4264(3)	4519(4)	7182(3)	74(2)
O(3)	4873(4)	3366(4)	9303(4)	95(2)
O(4)	4828(4)	4640(4)	9345(3)	90(2)
O(5)	3925(4)	6989(4)	9838(3)	84(2)
O(6)	3075(4)	4378(4)	5698(3)	89(2)
O(7)	4400(4)	4544(5)	4089(3)	96(2)
O(8)	2523(4)	4450(4)	3373(3)	84(2)
N(1)	4737(4)	6468(5)	8959(4)	77(2)
N(2)	4535(4)	3426(5)	7809(4)	72(2)
N(3)	4217(4)	3991(5)	5953(4)	78(2)
N(4)	3459(4)	4850(6)	4450(4)	82(2)
C(1)	4347(5)	5596(6)	7972(5)	68(2)
C(2)	3777(3)	5765(4)	8318(3)	82(3)
C(3)	3073(4)	5524(4)	8153(3)	84(3)
C(4)	2631(3)	5770(5)	8553(4)	115(4)
C(5)	2893(3)	6257(5)	9119(4)	103(4)
C(6)	3597(3)	6498(4)	9284(3)	83(3)
C(7)	4039(3)	6252(4)	8883(3)	74(3)
C(8)	5021(5)	6000(6)	8474(5)	75(3)
C(9)	4915(3)	6467(4)	7393(3)	80(3)
C(10)	5075(3)	6780(4)	6811(4)	87(3)
C(11)	4634(4)	6639(4)	6147(3)	88(3)
C(12)	4031(3)	6185(4)	6066(2)	86(3)
C(13)	3871(3)	5872(4)	6649(3)	69(2)
C(14)	4312(3)	6013(4)	7312(3)	82(3)
C(15)	4431(5)	4739(5)	7877(4)	68(2)
C(16)	4599(5)	4081(6)	8251(5)	80(3)
C(17)	4785(6)	4019(7)	9008(6)	87(3)

C(18)	4330(5)	3747(6)	7175(6)	81(3)
C(19)	4144(6)	3381(6)	6452(5)	78(3)
C(20)	4505(6)	2632(6)	6395(6)	85(3)
C(21)	4205(10)	2282(10)	5696(8)	142(6)
C(22)	5294(7)	2748(7)	6515(6)	100(4)
C(23)	3676(5)	4452(6)	5644(5)	69(2)
C(24)	3845(6)	5069(6)	5170(5)	79(3)
C(25)	3649(7)	5894(7)	5352(5)	91(3)
C(26)	3766(5)	4603(5)	3983(4)	63(2)
C(27)	3207(5)	4388(5)	3273(5)	77(3)
C(28)	3303(6)	4908(7)	2691(5)	79(3)
C(29)	3230(8)	5764(9)	2859(8)	120(4)
C(30)	3945(8)	4778(9)	2474(8)	123(4)
C(31)	1501(6)	3781(5)	2157(5)	100(4)
C(32)	1296(6)	4541(6)	1791(7)	104(4)
C(33)	918(8)	3193(10)	1901(8)	145(6)
C(34)	2145(8)	2839(9)	3485(7)	141(7)
C(35)	2535(15)	2780(13)	4250(9)	219(13)
C(36)	2648(15)	2402(11)	3171(17)	227(14)
C(37)	1160(8)	4262(11)	3478(11)	164(8)
C(38)	476(10)	3899(14)	3531(14)	208(11)
C(39)	1327(16)	5070(12)	3745(14)	212(12)
C(40)	3560(7)	7265(10)	10317(8)	126(5)
C(41)	3812(5)	7972(4)	10655(4)	95(3)
C(42)	4089(5)	8546(6)	10317(4)	118(4)
C(43)	4276(5)	9254(5)	10640(7)	138(6)
C(44)	4187(5)	9389(5)	11300(7)	142(6)
C(45)	3910(6)	8815(7)	11638(4)	134(5)
C(46)	3723(5)	8106(6)	11315(4)	110(4)
Cl(1)	2755(5)	3628(4)	878(3)	133(3)
Cl(2)	2424(5)	5208(5)	639(4)	141(3)
Cl(3)	3492(4)	4592(6)	157(7)	172(4)
C(1S)	2698(7)	4385(6)	316(8)	125(11)
Cl(4)	1845(5)	5304(7)	5786(6)	164(4)
Cl(5)	1064(6)	5554(7)	6790(5)	165(3)
Cl(6)	346(4)	5406(7)	5310(5)	152(3)

C(2S)	1091(6)	5649(15)	5944(6)	174(17)

Table 3. Bond lengths [Å] and angles [°] for k08308.

Si(1)-O(8)	1.694(8)
Si(1)-C(31)	1.847(10)
Si(1)-C(37)	1.852(18)
Si(1)-C(34)	1.875(16)
O(1)-C(9)	1.328(8)
O(1)-C(8)	1.458(12)
O(2)-C(18)	1.347(13)
O(2)-C(15)	1.387(11)
O(3)-C(17)	1.266(13)
O(4)-C(17)	1.260(13)
O(5)-C(6)	1.404(8)
O(5)-C(40)	1.419(15)
O(6)-C(23)	1.215(10)
O(7)-C(26)	1.205(11)
O(8)-C(27)	1.407(12)
N(1)-C(7)	1.383(9)
N(1)-C(8)	1.479(12)
N(2)-C(18)	1.336(13)
N(2)-C(16)	1.423(13)
N(3)-C(23)	1.337(13)
N(3)-C(19)	1.485(13)
N(4)-C(26)	1.306(12)
N(4)-C(24)	1.477(13)
C(1)-C(14)	1.485(10)
C(1)-C(2)	1.488(10)
C(1)-C(15)	1.515(14)
C(1)-C(8)	1.585(14)
C(2)-C(3)	1.3900
C(2)-C(7)	1.3900
C(3)-C(4)	1.3900

C(4)-C(5)	1.3900
C(5)-C(6)	1.3900
C(6)-C(7)	1.3900
C(9)-C(10)	1.3900
C(9)-C(14)	1.3900
C(10)-C(11)	1.3900
C(11)-C(12)	1.3900
C(12)-C(13)	1.3900
C(12)-C(25)	1.503(11)
C(13)-C(14)	1.3900
C(15)-C(16)	1.354(14)
C(16)-C(17)	1.454(14)
C(18)-C(19)	1.523(15)
C(19)-C(20)	1.499(15)
C(20)-C(21)	1.485(17)
C(20)-C(22)	1.509(17)
C(23)-C(24)	1.521(14)
C(24)-C(25)	1.551(16)
C(26)-C(27)	1.580(13)
C(27)-C(28)	1.520(13)
C(28)-C(30)	1.451(17)
C(28)-C(29)	1.54(2)
C(31)-C(32)	1.508(10)
C(31)-C(33)	1.512(10)
C(34)-C(36)	1.506(11)
C(34)-C(35)	1.511(11)
C(37)-C(38)	1.505(11)
C(37)-C(39)	1.505(11)
C(40)-C(41)	1.422(17)
C(41)-C(42)	1.3900
C(41)-C(46)	1.3900
C(42)-C(43)	1.3900
C(43)-C(44)	1.3900
C(44)-C(45)	1.3900
C(45)-C(46)	1.3900
Cl(1)-C(1S)	1.711(9)

Cl(2)-C(1S)	1.711(10)
Cl(3)-C(1S)	1.704(10)
Cl(4)-C(2S)	1.696(10)
Cl(5)-C(2S)	1.706(10)
Cl(6)-Cl(6)#1	1.564(18)
Cl(6)-C(2S)	1.704(10)

O(8)-Si(1)-C(31)	111.6(4)
O(8)-Si(1)-C(37)	101.5(5)
C(31)-Si(1)-C(37)	108.3(7)
O(8)-Si(1)-C(34)	109.5(5)
C(31)-Si(1)-C(34)	111.3(6)
C(37)-Si(1)-C(34)	114.2(8)
C(9)-O(1)-C(8)	108.0(7)
C(18)-O(2)-C(15)	106.6(7)
C(6)-O(5)-C(40)	121.7(8)
C(27)-O(8)-Si(1)	127.1(6)
C(7)-N(1)-C(8)	108.2(7)
C(18)-N(2)-C(16)	101.8(8)
C(23)-N(3)-C(19)	121.8(8)
C(26)-N(4)-C(24)	124.2(9)
C(14)-C(1)-C(2)	116.8(7)
C(14)-C(1)-C(15)	110.4(7)
C(2)-C(1)-C(15)	111.7(8)
C(14)-C(1)-C(8)	100.0(7)
C(2)-C(1)-C(8)	102.8(7)
C(15)-C(1)-C(8)	114.4(8)
C(3)-C(2)-C(7)	120.0
C(3)-C(2)-C(1)	130.4(6)
C(7)-C(2)-C(1)	109.5(6)
C(2)-C(3)-C(4)	120.0
C(5)-C(4)-C(3)	120.0
C(4)-C(5)-C(6)	120.0
C(7)-C(6)-C(5)	120.0
C(7)-C(6)-O(5)	114.4(5)
C(5)-C(6)-O(5)	125.6(5)

N(1)-C(7)-C(6)	127.0(5)
N(1)-C(7)-C(2)	113.0(5)
C(6)-C(7)-C(2)	120.0
O(1)-C(8)-N(1)	111.8(8)
O(1)-C(8)-C(1)	107.1(7)
N(1)-C(8)-C(1)	105.0(7)
O(1)-C(9)-C(10)	125.1(5)
O(1)-C(9)-C(14)	114.3(5)
C(10)-C(9)-C(14)	120.0
C(9)-C(10)-C(11)	120.0
C(10)-C(11)-C(12)	120.0
C(11)-C(12)-C(13)	120.0
C(11)-C(12)-C(25)	119.3(6)
C(13)-C(12)-C(25)	119.3(6)
C(14)-C(13)-C(12)	120.0
C(13)-C(14)-C(9)	120.0
C(13)-C(14)-C(1)	128.5(6)
C(9)-C(14)-C(1)	109.8(5)
C(16)-C(15)-O(2)	105.8(8)
C(16)-C(15)-C(1)	141.1(8)
O(2)-C(15)-C(1)	113.0(8)
C(15)-C(16)-N(2)	111.5(7)
C(15)-C(16)-C(17)	126.0(10)
N(2)-C(16)-C(17)	122.5(9)
O(4)-C(17)-O(3)	122.5(9)
O(4)-C(17)-C(16)	116.7(10)
O(3)-C(17)-C(16)	120.7(10)
N(2)-C(18)-O(2)	114.2(9)
N(2)-C(18)-C(19)	130.6(10)
O(2)-C(18)-C(19)	115.1(9)
N(3)-C(19)-C(20)	115.8(9)
N(3)-C(19)-C(18)	107.0(8)
C(20)-C(19)-C(18)	115.8(9)
C(21)-C(20)-C(19)	110.5(10)
C(21)-C(20)-C(22)	109.3(11)
C(19)-C(20)-C(22)	110.8(10)

O(6)-C(23)-N(3)	124.1(10)
O(6)-C(23)-C(24)	120.4(9)
N(3)-C(23)-C(24)	115.4(8)
N(4)-C(24)-C(23)	106.3(8)
N(4)-C(24)-C(25)	111.7(8)
C(23)-C(24)-C(25)	113.4(8)
C(12)-C(25)-C(24)	116.1(9)
O(7)-C(26)-N(4)	123.5(9)
O(7)-C(26)-C(27)	124.5(8)
N(4)-C(26)-C(27)	112.0(9)
O(8)-C(27)-C(28)	112.3(8)
O(8)-C(27)-C(26)	108.0(8)
C(28)-C(27)-C(26)	110.0(7)
C(30)-C(28)-C(27)	115.4(10)
C(30)-C(28)-C(29)	110.7(11)
C(27)-C(28)-C(29)	111.7(9)
C(32)-C(31)-C(33)	110.4(10)
C(32)-C(31)-Si(1)	116.5(7)
C(33)-C(31)-Si(1)	113.6(9)
C(36)-C(34)-C(35)	100(2)
C(36)-C(34)-Si(1)	117.7(11)
C(35)-C(34)-Si(1)	118.3(13)
C(38)-C(37)-C(39)	118.5(19)
C(38)-C(37)-Si(1)	126.9(16)
C(39)-C(37)-Si(1)	114.6(11)
O(5)-C(40)-C(41)	115.8(13)
C(42)-C(41)-C(46)	120.0
C(42)-C(41)-C(40)	121.4(10)
C(46)-C(41)-C(40)	118.4(10)
C(43)-C(42)-C(41)	120.0
C(42)-C(43)-C(44)	120.0
C(45)-C(44)-C(43)	120.0
C(44)-C(45)-C(46)	120.0
C(45)-C(46)-C(41)	120.0
Cl(3)-C(1S)-Cl(2)	106.7(8)
Cl(3)-C(1S)-Cl(1)	112.4(9)

Cl(2)-C(1S)-Cl(1)	111.6(8)
Cl(6)#1-Cl(6)-C(2S)	165.6(9)
Cl(4)-C(2S)-Cl(6)	112.8(9)
Cl(4)-C(2S)-Cl(5)	114.1(11)
Cl(6)-C(2S)-Cl(5)	117.3(10)

Symmetry transformations used to generate equivalent atoms: #1 -x,y,-z+1

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for k08308.

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Si(1)	81(2)	86(2)	92(2)	-4(2)	24(1)	-9(2)
O(1)	90(4)	82(4)	81(4)	-8(4)	22(4)	-6(4)
O(2)	91(4)	55(4)	74(4)	2(3)	19(3)	6(3)
O(3)	134(6)	58(4)	94(5)	9(4)	31(4)	4(4)
O(4)	134(6)	61(4)	70(4)	1(3)	19(4)	9(4)
O(5)	90(4)	90(5)	80(4)	-22(4)	38(4)	2(4)
O(6)	101(5)	78(4)	87(4)	0(4)	22(4)	1(4)
O(7)	81(5)	126(6)	86(4)	-7(4)	31(3)	-2(4)
O(8)	77(4)	79(4)	96(4)	-18(4)	21(3)	-8(3)
N(1)	71(5)	80(5)	77(5)	-12(4)	17(4)	-6(4)
N(2)	78(5)	65(5)	80(5)	-4(4)	32(4)	-6(4)
N(3)	77(5)	76(5)	84(5)	-2(4)	24(4)	3(4)
N(4)	79(5)	98(6)	71(5)	8(4)	21(4)	-7(5)
C(1)	73(5)	70(6)	63(5)	4(4)	21(4)	14(5)
C(2)	86(7)	77(7)	77(6)	2(5)	11(5)	-4(6)
C(3)	85(7)	85(7)	87(6)	-3(6)	30(6)	7(6)
C(4)	73(7)	123(11)	143(10)	-49(9)	16(7)	-28(7)
C(5)	81(7)	128(10)	96(7)	0(8)	18(6)	-4(7)
C(6)	69(6)	96(8)	78(6)	-7(6)	10(5)	14(6)
C(7)	74(6)	70(6)	75(6)	19(5)	16(5)	16(5)
C(8)	86(6)	76(6)	66(5)	-1(5)	23(5)	-4(5)
C(9)	99(7)	74(6)	74(6)	-5(5)	32(6)	9(6)
C(10)	96(7)	53(6)	118(8)	1(5)	40(7)	-15(5)

C(11)	96(8)	74(7)	96(8)	9(6)	28(6)	11(6)
C(12)	83(7)	74(6)	96(7)	-4(6)	18(6)	6(6)
C(13)	76(6)	68(6)	63(5)	4(4)	21(5)	5(5)
C(14)	83(7)	87(7)	76(7)	-7(5)	22(5)	9(6)
C(15)	83(6)	62(6)	63(5)	-13(4)	27(4)	-4(5)
C(16)	89(7)	78(7)	71(6)	14(6)	18(5)	5(5)
C(17)	106(8)	73(8)	86(7)	0(6)	33(6)	7(6)
C(18)	90(7)	62(6)	88(7)	-5(5)	17(5)	3(5)
C(19)	98(7)	68(6)	63(5)	8(5)	15(5)	0(5)
C(20)	103(8)	67(6)	87(7)	3(5)	30(6)	15(6)
C(21)	170(14)	127(12)	109(9)	-48(9)	5(9)	33(10)
C(22)	117(10)	84(8)	107(8)	4(6)	44(7)	22(7)
C(23)	42(5)	71(6)	97(6)	-23(5)	24(4)	-11(5)
C(24)	93(7)	76(7)	66(6)	3(5)	21(5)	-5(5)
C(25)	117(8)	93(8)	57(5)	5(5)	14(5)	-6(7)
C(26)	72(6)	61(5)	65(5)	5(4)	34(4)	8(5)
C(27)	88(7)	47(5)	97(7)	-7(5)	25(5)	-28(5)
C(28)	90(7)	91(7)	61(5)	17(5)	27(5)	7(5)
C(29)	132(11)	101(10)	138(11)	38(8)	54(9)	10(8)
C(30)	142(11)	103(9)	141(11)	8(8)	68(9)	-16(9)
C(31)	119(9)	84(7)	83(6)	-30(6)	3(6)	16(7)
C(32)	81(7)	92(8)	127(9)	19(7)	9(6)	2(6)
C(33)	124(11)	159(15)	128(11)	12(11)	-9(9)	-51(11)
C(34)	115(10)	129(13)	151(13)	47(11)	-13(10)	-38(10)
C(35)	280(30)	132(17)	189(19)	-1(15)	-39(19)	-86(18)
C(36)	230(20)	91(12)	410(40)	46(18)	170(30)	64(14)
C(37)	93(9)	220(20)	178(14)	-7(15)	40(9)	-56(12)
C(38)	180(20)	129(15)	280(30)	9(18)	8(18)	-58(15)
C(39)	290(30)	153(18)	260(20)	-100(18)	190(20)	-51(19)
C(40)	92(8)	146(13)	128(10)	-45(10)	8(7)	37(8)
C(41)	96(8)	75(7)	115(9)	-6(7)	32(7)	17(6)
C(42)	114(9)	131(13)	102(8)	5(9)	16(7)	-24(9)
C(43)	102(10)	77(10)	226(19)	1(11)	29(11)	-12(7)
C(44)	126(12)	92(11)	191(17)	-65(12)	13(11)	13(9)
C(45)	117(10)	158(16)	118(10)	-24(12)	15(8)	23(11)
C(46)	116(9)	107(10)	105(9)	-14(8)	25(7)	2(8)

Cl(1)	193(7)	94(5)	96(4)	2(3)	9(4)	-40(5)
Cl(2)	173(7)	119(6)	134(5)	1(5)	49(5)	5(5)
Cl(3)	110(5)	146(8)	286(12)	46(8)	99(7)	26(5)
C(1S)	101(16)	200(30)	67(11)	-22(16)	14(11)	-80(20)
Cl(4)	132(6)	144(7)	220(9)	-50(7)	54(6)	-5(6)
Cl(5)	180(8)	179(9)	137(6)	-20(6)	41(6)	-18(7)
Cl(6)	107(5)	177(8)	171(7)	11(7)	36(4)	3(5)
C(2S)	180(30)	130(30)	260(40)	-90(30)	140(30)	-40(20)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for k08308.

	x	y	z	U(eq)
H(3)	4976	3425	9738	143
H(4)	4938	4543	9775	135
H(1A)	4971	6823	9246	92
H(3B)	4628	4051	5858	94
H(4B)	2993	4888	4328	99
H(3A)	2894	5191	7766	101
H(4A)	2150	5605	8440	139
H(5A)	2592	6425	9392	123
H(8A)	5367	5608	8735	91
H(10A)	5487	7091	6866	105
H(11A)	4744	6853	5749	106
H(13A)	3459	5562	6593	82
H(19A)	3625	3261	6338	93
H(20A)	4426	2270	6758	102
H(21A)	4455	1800	5663	213
H(21B)	4265	2640	5334	213
H(21C)	3699	2177	5629	213
H(22A)	5521	2251	6482	150
H(22B)	5495	2969	6979	150

H(22C)	5379	3100	6160	150
H(24A)	4366	5053	5212	94
H(25A)	3745	6254	5002	109
H(25B)	3132	5910	5306	109
H(27A)	3287	3842	3153	93
H(28A)	2898	4791	2275	95
H(29A)	2791	5841	3000	180
H(29B)	3214	6075	2444	180
H(29C)	3638	5921	3241	180
H(30A)	4014	4223	2427	184
H(30B)	4354	4992	2823	184
H(30C)	3902	5030	2023	184
H(31A)	1908	3591	1987	120
H(32A)	1133	4456	1286	156
H(32B)	1708	4885	1897	156
H(32C)	912	4775	1952	156
H(33A)	775	3189	1389	218
H(33B)	509	3328	2073	218
H(33C)	1093	2682	2074	218
H(34A)	1708	2516	3413	169
H(35A)	2650	2239	4371	329
H(35B)	2233	2980	4531	329
H(35C)	2974	3081	4344	329
H(36A)	2753	1899	3401	340
H(36B)	3090	2695	3237	340
H(36C)	2429	2326	2671	340
H(37A)	913	4468	3006	197
H(38A)	194	4282	3701	312
H(38B)	583	3465	3857	312
H(38C)	207	3716	3069	312
H(39A)	922	5280	3888	318
H(39B)	1420	5392	3375	318
H(39C)	1748	5065	4147	318
H(40A)	3589	6866	10680	152
H(40B)	3053	7329	10065	152
H(42A)	4150	8454	9866	142

H(43A)	4465	9647	10409	165
H(44A)	4315	9873	11521	171
H(45A)	3849	8906	12089	161
H(46A)	3534	7714	11546	133
H(1S)	2346	4254	-136	150
H(2S)	1129	6218	5886	209

Table 6. Hydrogen bonds for k08308 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(3)-H(3)...O(3)#2	0.84	1.85	2.681(15)	168.8
O(4)-H(4)...O(4)#2	0.84	1.69	2.507(13)	162.8
N(1)-H(1A)...O(5)#2	0.88	2.44	3.164(10)	140.3
N(3)-H(3B)...O(7)#3	0.88	2.06	2.891(12)	157.1
N(4)-H(4B)...O(8)	0.88	2.02	2.511(10)	113.9

Symmetry transformations used to generate equivalent atoms:
#1 -x,y,-z+1 #2 -x+1,y,-z+2 #3 -x+1,y,-z+1

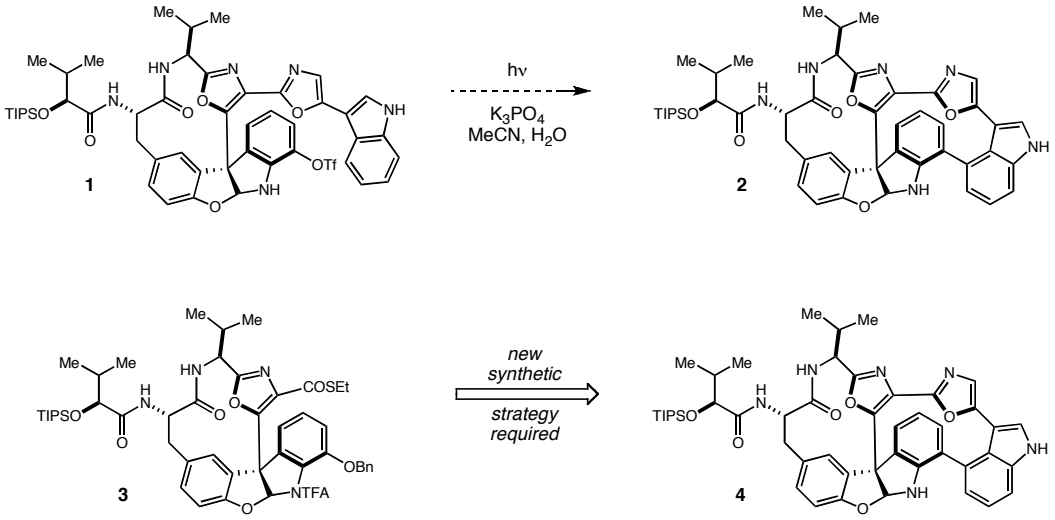
Chapter 5

Third-Generation MacMillan Synthesis of Diazonamide A

I. Development of a New Synthetic Strategy

As described at the conclusion of the previous chapter, closure of the right-hand macrocycle of diazonamide A through a late-stage photocyclization proved unachievable, despite several highly analogous precedents (Figure 1). Undaunted, we sought to investigate and develop alternative approaches to creating this complicated substructure. To take full advantage of our prior success in closing the left-hand portion of the target molecule, we chose to begin our new investigations from thioester **3**, an intermediate from our previous studies.

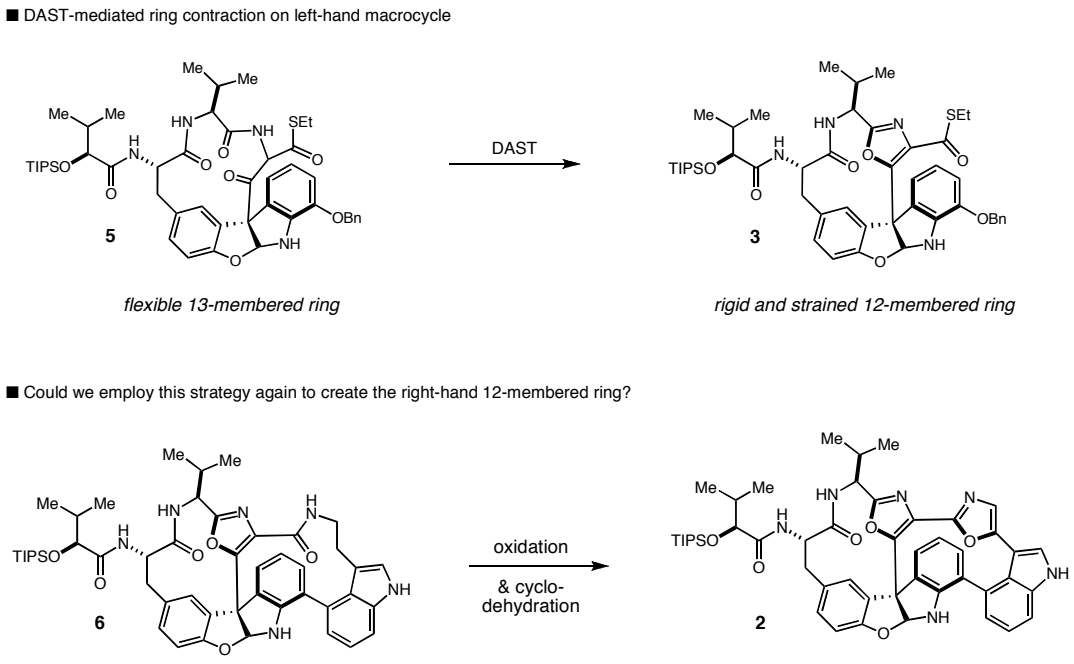
Figure 1: Failed Witkop cyclization necessitates new solutions



The highly strained nature of the unusual right-hand ring system made us circumspect of any disconnection leading to direct annulation of the intact ring. Rather,

we chose to revisit our previous strategy of first creating a larger, conformationally flexible ring and then subsequently contracting it to the desired size (Figure 2). This approach had proven uniquely successful in our efforts to close the left-hand macrocycle of diazonamide A, and its use had the additional appeal of providing a pleasing conceptual symmetry to our synthesis.

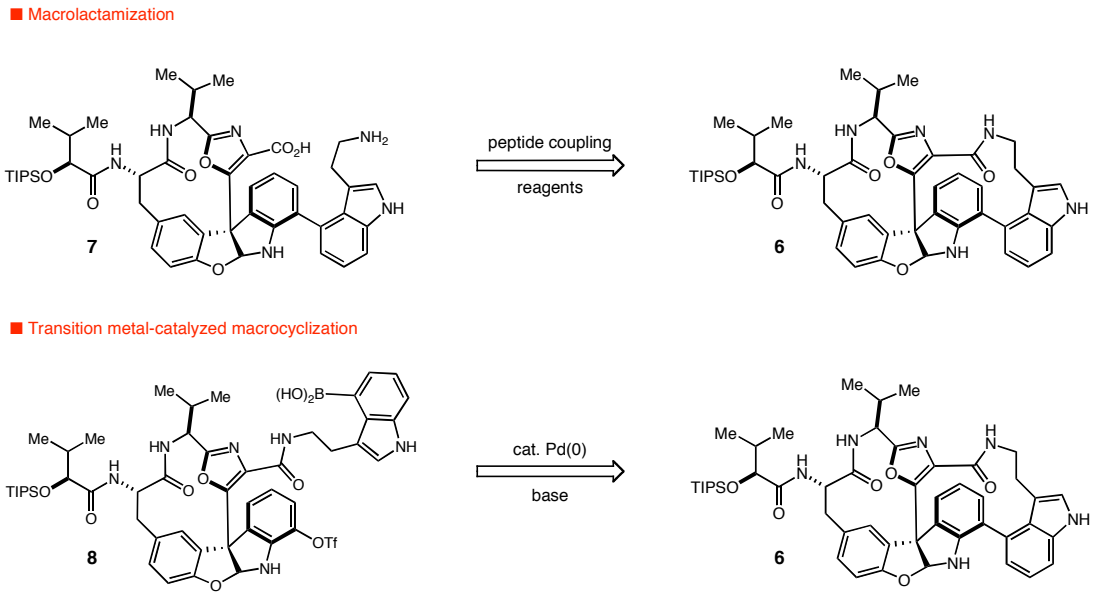
Figure 2: Strategies for the synthesis of the right-hand macrocycle



Application of this strategy to the system at hand was straightforward. Working retrosynthetically from the intact macrocycle **2**, we postulated that the ring contraction step would be most easily applied to the cyclodehydration of the B-ring oxazole, leading to a target structure such as **6** (Figure 2). Amide **6** could then be synthesized by the appendage of a suitably substituted tryptamine unit onto an appropriate derivative of thioester **3** and closure of the D-E biaryl bond.

Choosing to install the tryptamine unit intact, we were presented with two limiting possibilities for accomplishing these two bond constructions in the synthesis of **6** (Figure 3). The first would be to initially form the D-E biaryl bond in an intermolecular process and then attempt a macrolactamization. Alternatively the intermolecular amide bond could be created first, followed by intramolecular ring-closing biaryl formation.

Figure 3: Limiting possibilities for the synthesis of the hydrated right-hand macrocycle

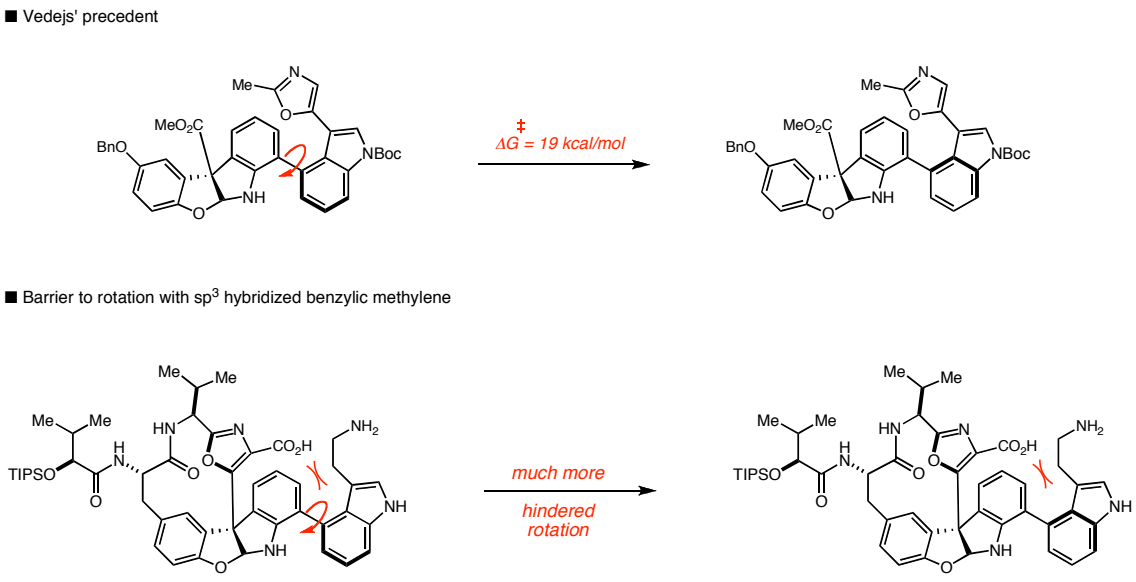


Examining both scenarios on the basis of practicality and precedence indicated that the macrolactamization approach was unsound. Prior work from the Vedejs group illustrated that palladium-catalyzed cross coupling produced the D-E biaryl as a 1:1 mixture of atropisomers and that the kinetic barrier to their interconversion was roughly 20 kcal/mol when the indole 3' benzylic carbon is sp^2 hybridized (Figure 4).[1] However, with an sp^3 hybridized methylene group in the benzylic position, such as we required, the barrier would likely be substantially higher, if not impossible in a synthetically

[1] Zajac, M. A.; Vedejs, E. *Org. Lett.* **2004**, *6*, 237–240.

reasonable temperature regime. This suggested the likelihood that lactamization would likely affect a resolution of the atropisomers resulting from intermolecular biaryl formation, rendering half of a precious late-stage intermediate unusable. In light of this possibility, we elected to pursue an approach of intermolecular amide formation followed by intramolecular biaryl formation as the key ring-closing event.

Figure 4: Barriers to rotation around D-E biaryl axis



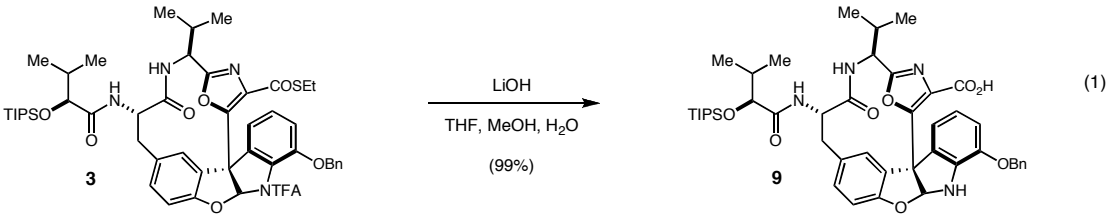
A palladium-catalyzed Suzuki coupling was chosen as the preferred methodology to form the desired D-E biaryl bond. This reaction has been used often in the synthesis of large rings and the reaction conditions are suitably mild for complex substrates.[2] Secondly, this bond construction could utilize the phenol already present in the benzyl ether of **3** as its corresponding triflate. But perhaps most importantly, the 4-indole boronic ester **8** was predicted to be synthetically robust. This was deemed an essential attribute, as the boron functionality would have to survive intact through several

[2] For several examples of the use of Suzuki coupling in the synthesis of large ring biaryls, see: (a) Elder, A. M.; Rich, D. H. *Org. Lett.* **1999**, *1*, 1443–1446. (b) Carbonnelle, A. C.; Zhu, J. *Org. Lett.* **2000**, *2*, 3477–3480. (c) Boi-Choussy, M.; Cristau, P.; Zhu, J. *Angew. Chem. Int. Ed.* **2003**, *42*, 4238–4241.

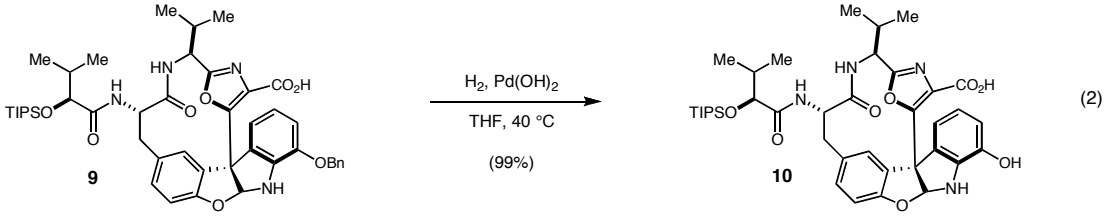
transformations prior to its actual use. With this ring contraction strategy and associated retrosynthetic analysis in hand, we were ready to evaluate their viability.

II. Third-Generation Synthesis

In the forward direction our new synthesis begins with the hydrolysis of the ethyl thioester and trifluoroacetamide of **3** under the action of aqueous lithium hydroxide (eq 1). This was followed by hydrogenolysis of the benzyl ether of **9** with Pearlman's catalyst, providing phenol **10** in 99% yield (eq 2). This two-step procedure provides rapid and nearly quantitative access to key building block **10**, from which we would investigate our new annulation strategy.



(1)

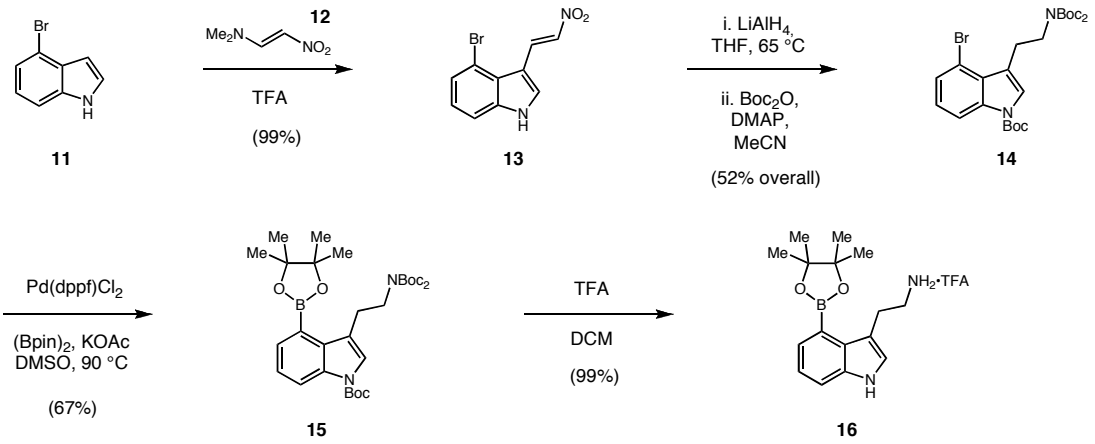


(2)

The synthesis of the 4-boronic ester tryptamine component commences with the known reaction of 4-bromoindole **11** and nitroalkene **12** in neat trifluoroacetic acid to yield **13** in quantitative yield (Scheme 1). **13** is then reduced to its corresponding saturated amine by treatment with excess lithium aluminum hydride in refluxing THF, as

had been previously described by Nicolaou.[3] The resulting amine product is then exhaustively acylated with excess Boc_2O in acetonitrile under DMAP catalysis to provide triscarbamate **14** in 52% yield over two steps. The resulting aryl bromide of **14** is then transformed into its corresponding (pinacolato)boronic ester **15** through a palladium-catalyzed Suzuki-Miyaura borylation and the carbamate protecting groups were removed with TFA to yield the desired tryptamine **16** in a scalable five-step sequence.

Scheme 1: Synthesis of 4-boronic ester tryptamine



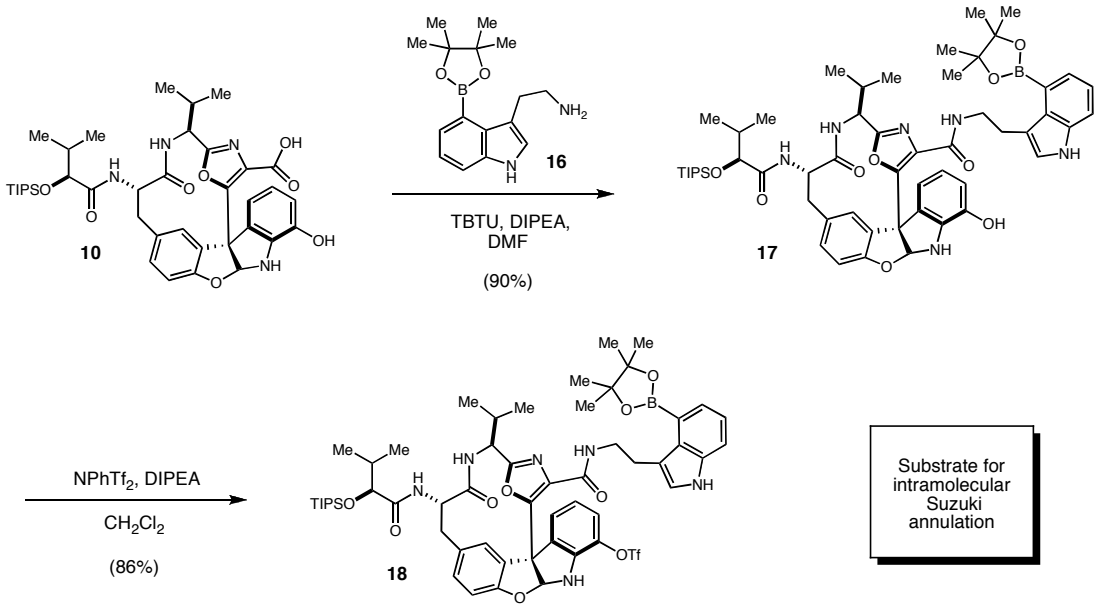
With fragments **10** and **16** in hand, we were able to investigate the amide bond formation necessary to join them together. This was readily accomplished, with the use of TBTU and HOBT in DMF proving optimal, providing the desired amide product **17** in 90% yield (Scheme 2).[4] Following intermolecular amide formation, the resulting phenol was then transformed into its corresponding aryl triflate in 86% yield using $NPhTf_2$ to provide key intermediate **18** for our proposed Suzuki macrocyclization. Gratifyingly, no

[3] Nicolaou, K. C.; Snyder, S. A.; Huang, X.; Simonsen, K. B.; Koumbis, A. E.; Bigot, A. *J. Am. Chem. Soc.* **2004**, *126*, 10162–10173.

[4] The efficiency of this process was strongly dependent on the quality of the coupling agent and optimal results were only obtained using fresh TBTU.

protodeborylation of the boronic ester functionality was observed during carbamate deprotection, peptide coupling, or triflate formation.

Scheme 2: Synthesis of Suzuki macrocyclization precursor

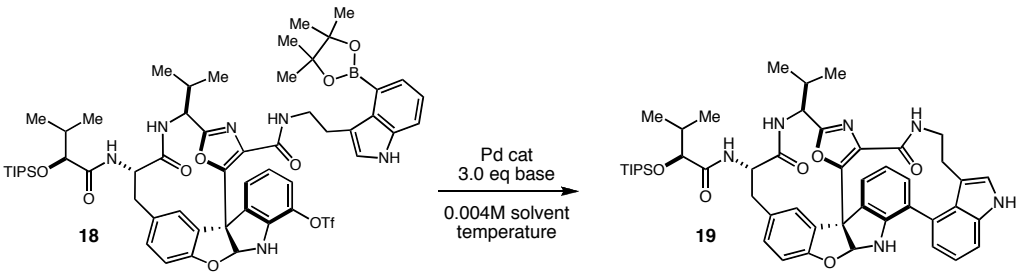


With **18** in hand, we were now situated to explore the key intramolecular Suzuki reaction to close the right-hand 13-membered ring. While Suzuki couplings are a mainstay technology in the synthesis of biaryls, their success is often highly dependent on every reaction variable, including the composition of the solvent mixtures, base, palladium source, ligand, temperature, and concentration.[5] This makes exhaustive optimization a time consuming and materially expensive process, which can be especially daunting when conducted at an advanced stage of a synthesis with precious intermediates. In light of these considerations, we conducted a modest survey of initial reaction conditions, with the hope that a promising lead would develop which could be optimized further.

[5] Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483.

Selected results of this initial screening are listed below in Table 1. $Pd(PPh_3)_4$ was initially found to be an effective catalyst for the desired transformation (Table 1, entry 4). Evaluation of the base demonstrated that potassium salts were most effective, and that K_3PO_4 was optimal in terms of yield. A mixed dioxane/water solvent system provided the greatest level of conversion, providing the desired adduct **19** in 53% when heated to 70 °C for one hour. Though modest, this yield was serviceable and allowed subsequent downstream chemistry to be examined. Moreover, closure of this macrocycle signaled that a substantial fraction of our synthetic strategy had been successfully executed, providing a firm footing for both planning and investigating all subsequent approaches to this substructure.

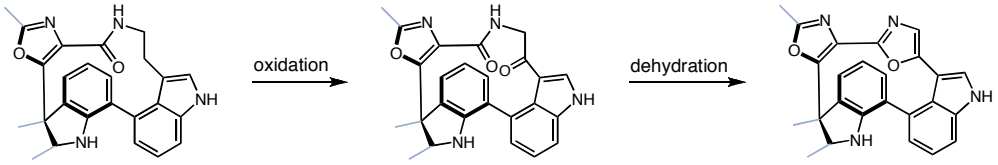
Table 1: Optimization of intramolecular Suzuki coupling



Entry	Pd Source	Base	Temp (°C)	Solvent	Yield
1	$Pd(dppf)Cl_2$	K_3PO_4	60	THF/H_2O	0%
2	$Pd(PPh_3)_4$	KF	80	dioxane	0%
3	$Pd(PPh_3)_4$	KOAc	60	$dioxane/H_2O$	trace
4	$Pd(PPh_3)_4$	K_3PO_4	60	$PhH/MeOH/H_2O$	10%
5	$Pd(PPh_3)_4$	K_3PO_4	60	$toluene/H_2O$	trace
6	$Pd(PPh_3)_4$	K_3PO_4	60	DME/MeOH	trace
7	$Pd(PPh_3)_4$	K_3PO_4	60	THF/H_2O	5%
8	$Pd(PPh_3)_4$	K_3PO_4	60	$dioxane/H_2O$	36%
9	$Pd(PPh_3)_4$	K_3PO_4	70	$dioxane/H_2O$	53%

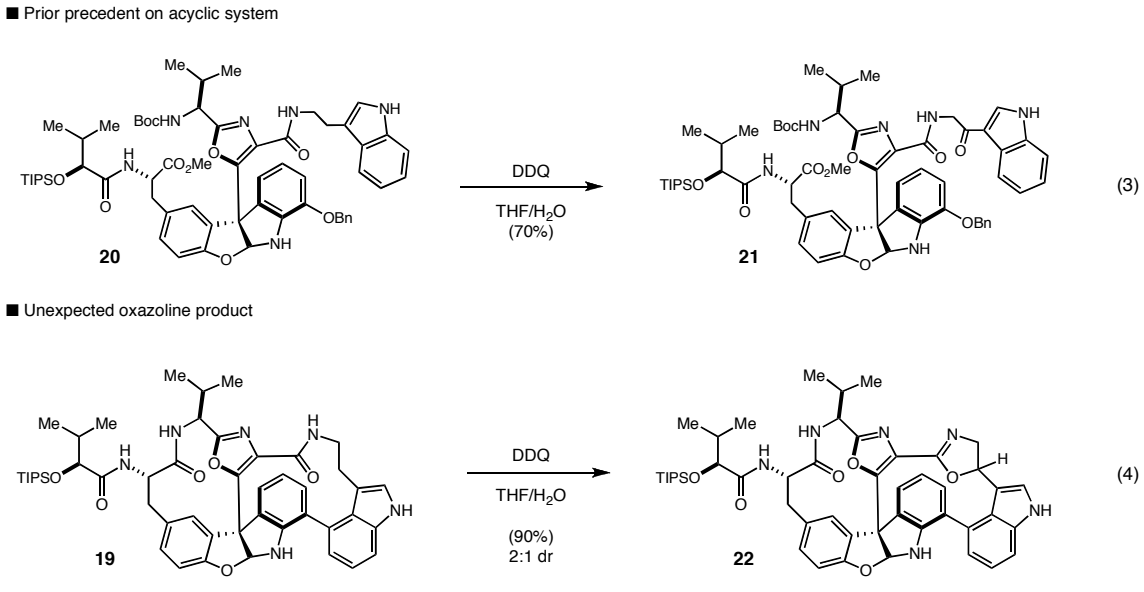
We were now positioned to evaluate our proposed ring-contraction. Toward this end, we would need to oxidize the benzylic methylene of our tryptamine fragment of **19** to its corresponding ketone, followed by cyclodehydration of the resulting ketoamide to furnish the desired bisoxazole (Figure 5).

Figure 5: Benzylic oxidation route to the keto-amide necessary to form the desired oxazole



In our previous work on an analogous acyclic substrate **20**, this transformation was easily performed with DDQ in aqueous THF (Figure 6). However, when **19** was exposed to these conditions, the sole product was oxazoline **22**, resulting from the intramolecular trapping of the transient cation by the pendant amide carbonyl in a process mechanistically related to the well-known Yonemitsu oxidation.[6]

Figure 6: Benzylic oxidation of tryptamine



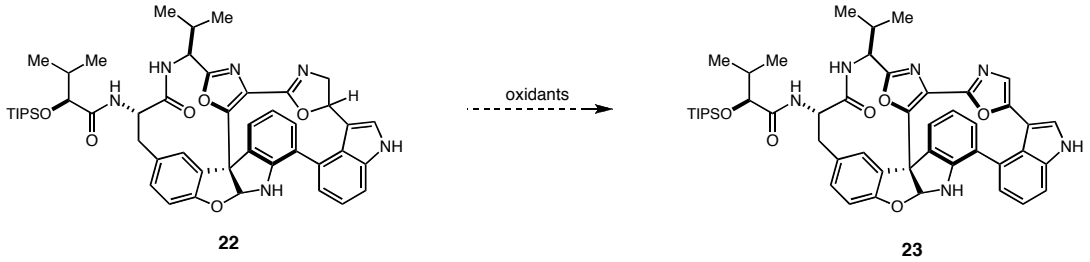
[6] Oikawa, Y.; Yonemitsu, Y. *J. Org. Chem.* **1977**, *42,* 1213–1216.

The observation that the amide carbonyl was kinetically able to outcompete the water in solution in quenching the carbocation is likely the result of the conformational constraints inherent to the large ring that effectively lock this internal nucleophile in close proximity to the oxidatively generated cation. This stands in sharp contrast to the high yield of aryl ketone **21** observed upon subjection of a highly analogous acyclic substrate (**20**) to identical reaction conditions (eq 3). Yet, though unexpected, this oxazoline formation had accomplished our desired ring contraction and this functionality had only to be dehydrogenated to yield the intact right-hand macrocycle.

Oxidations of dihydroheteroaromatics to their corresponding arenes are well known in the literature, and an abundance of conditions have been reported to affect these transformations. Thus, we were optimistic that this type of oxidation would also be suitable to our purposes and readily accomplished. However, all the known cases of oxidizing 4,5 dihydrooxazoles, such as **22**, to their corresponding fully aromatic congeners required the presence of an electron withdrawing group at the 4-position of the ring.[7] Yet, being so close to finishing the total synthesis and faced with no other readily apparent options, we pushed onward and attempted to apply the most commonly used conditions to affect this general type of transformation to **22**. Heterogeneous metal oxidants, such as MnO_2 or Pd/C and O_2, were evaluated first, but despite extensive efforts these reagents all proved unsuccessful, providing only recovered starting material and unidentifiable decomposition products. Furthermore, treatment with oxidants such as DDQ or CAN also failed to deliver any of the desired oxazole **23**.

[7] (a) Barrish, J. C.; Singh, J.; Sperel, S. H.; Han, W. C.; Kissick, T. P.; Kronenthal, D. R.; Mueller, R. H. *J. Org. Chem*. **1993**, *58*, 4494–4496. (b) Tavares, F.; Meyers, A. I. *Tet. Lett.* **1994**, *35*, 6803–6806.

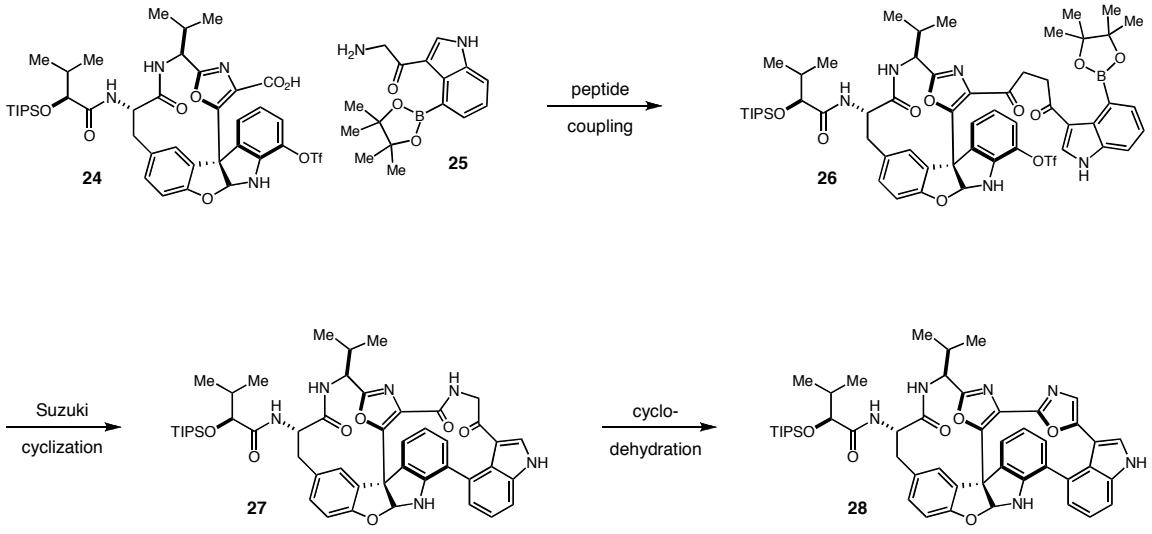
Figure 7: Attempted dehydrogenation of oxazoline



III. A Second Approach

Thus, faced with the seeming reluctance of substrate **22** to undergo the desired oxidation event, we decided to reevaluate our strategy. Being unable to install either the aryl ketone functionality necessary for cyclodehydration or to dehydrogenate the oxazoline functionality, we chose to synthesize tryptamine **25**, where the benzylic carbon was already in the desired ketone oxidation state (Figure 8). This could then be coupled

Figure 8: New retrosynthesis of the right-hand macrocycle

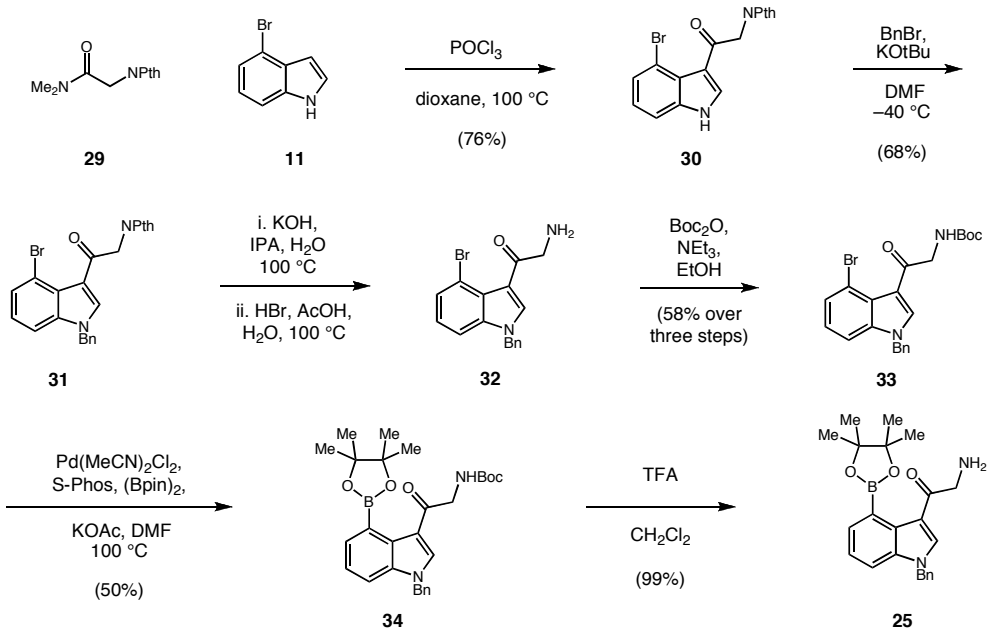


to carboxylic acid **24** as described above and subjected to ring-closing Suzuki coupling. Following biaryl formation, the ring of **27** could then be contracted through

cyclodehydration using any one of a variety of conditions to yield the intact right-hand macrocycle **28**.

In the forward sense, the synthesis of **25** commences with a Vilsmeier-Hack acylation between the valine-derived dimethylamide **29** and 4-bromoindole **12** under the action of $POCl_3$ in refluxing dioxane, to yield the desired aryl ketone **30** in 76% yield following hydrolysis (Scheme 3).[8] The N-H bond of this acylindole product was deemed too acidic not to interfere in subsequent synthetic steps and was accordingly protected with benzyl bromide to yield ketone **31**. The phthalimide group was then removed by a two-step protocol involving treatment first with a refluxing solution of aqueous KOH in isopropanol followed by refluxing the resulting product in an aqueous solution of HBr and AcOH. The resulting free amine **32** was then protected as its Boc-carbamate (**33**) and

Scheme 3: Synthesis of 4-boronic ester 3′-oxotryptamine



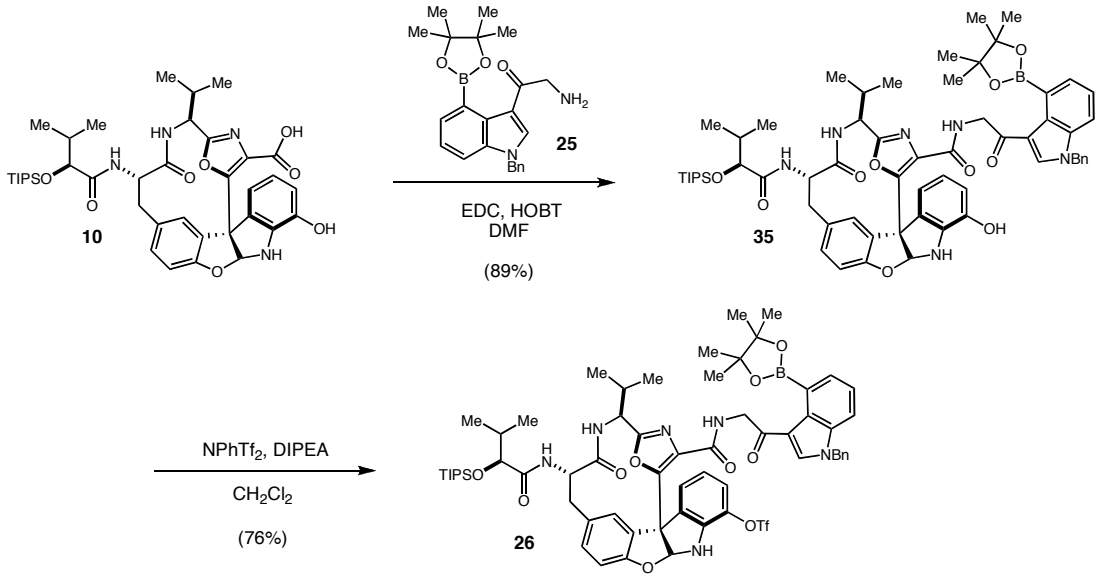
subjected to Suzuki-Miyaura borylation to install the requisite 4-(pinacolato)boronic

[8] Kreisberg, J. D.; Magnus, P.; McIver, E. G. *Tet. Lett.* **2001**, *42*, 627–629.

ester. The *tert*-butyl carbamate of **34** was then removed through protonolysis to yield the desired fragment **25** in a straightforward and scalable seven-step sequence.

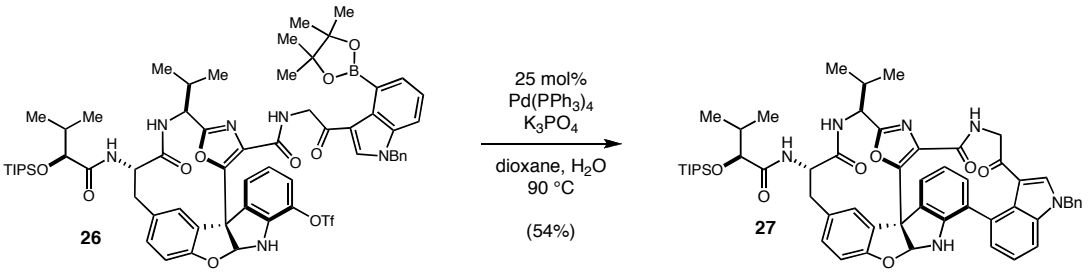
Tryptamine fragment **25** was then coupled to carboxylic acid **10** using EDC and HOBT to provide amide **35** in 89% yield (Scheme 4). The phenol was then converted to triflate **26** upon treatment with $NPhTf_2$ to yield the precursor for the desired Suzuki macrocyclization.

Scheme 4: Synthesis of second-generation Suzuki macrocyclization precursor



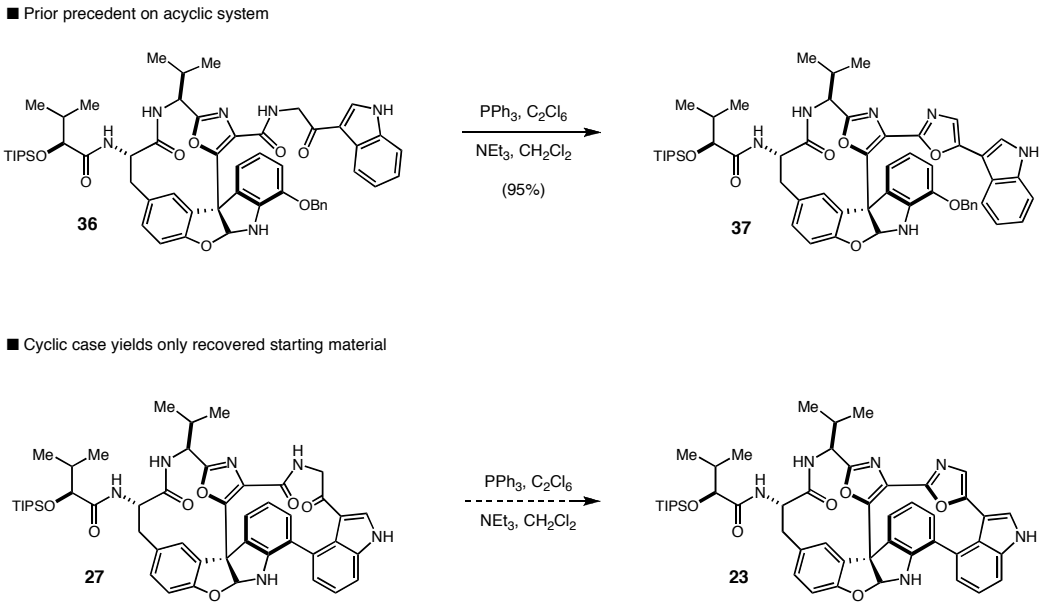
We found that the reaction conditions optimized for the previously described Suzuki macrocyclization were also effective for **26**, providing the 13-membered ring of product **27** in 36% yield. However, with optimization it was discovered that when the reaction temperature was raised to 90 °C the product was produced in a more acceptable 54% yield (Figure 9). Notably, even with this relatively high reaction temperature and the presence of a reasonably strong aqueous base, no epimerization of the amino acid-derived stereocenters was observed.

Figure 9: Suzuki macrocyization with oxotryptamine



We then set out to attempt the proposed cyclodehydration of **27** using the chlorophosphonium-mediated conditions reported by Wipf and coworkers that had been effective in cyclizing an acyclic analogue (**36**) (Figure 10).[9] However, treatment of **27** under these conditions only returned the starting material, even when a vast excess of reagent was employed. Likewise, treatment with other standard cyclodehydrating conditions, such as $POCl_3$ in pyridine or strong mineral acids, produced none of the

Figure 10: Failed cyclodehydration using Wipf conditions



desired oxazole **23**. The reasons for the failure of these reagents to act on **27** are not

[9] Wipf, P.; Miller, C. P. *J. Org. Chem.* **1993**, *58*, 3604–3606.

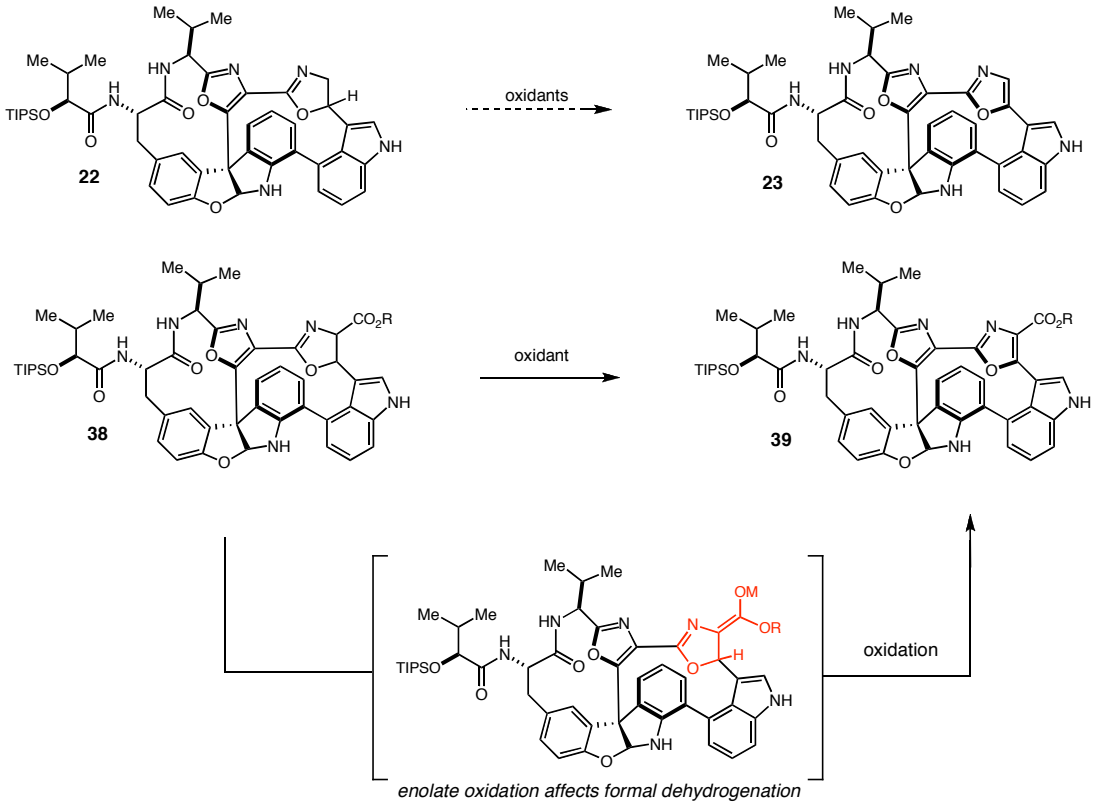
clearly apparent, however it seemed that this second approach had reached an irresolvable impasse and was subsequently abandoned in favor of a new approach.

IV. A Third Approach

Having again come within a single transformation of the certain completion of our total synthesis of diazonamide A, we were obliged to regroup and devise a new path forward. We remained confident that our overarching ring-contraction strategy was viable, given our success in forming the ring-contracted oxazoline **22** (Figure 11). However, we had found this unfunctionalized form of the heterocycle could not be successfully dehydrogenated due to the severe constraints associated with adopting the stereoelectronically required coplanar confirmation required to form the requisite benzylic oxocarbenium within the oxazoline-containing macrocyclic framework. However, we reasoned that this constraint could be bypassed if the homobenzylic methylene of the oxazoline was to undergo oxidation instead. This could be most readily accomplished if the carbon in question was conjugated to a stabilizing functionality external to the macrocyclic framework.

There are many known examples of dehydrogenating 4-acyloxazolines under oxidizing conditions, presumably through oxidation of the relatively electron-rich enol or enolate form of the substrate. This suggests that incorporation of a carbonyl group at the homobenzylic position of our tryptamine backbone would provide a secondary avenue by which to create the requisite oxazole ring without having to access a highly disfavored conformation (Figure 11). We envisioned that the carbonyl functionality could then be

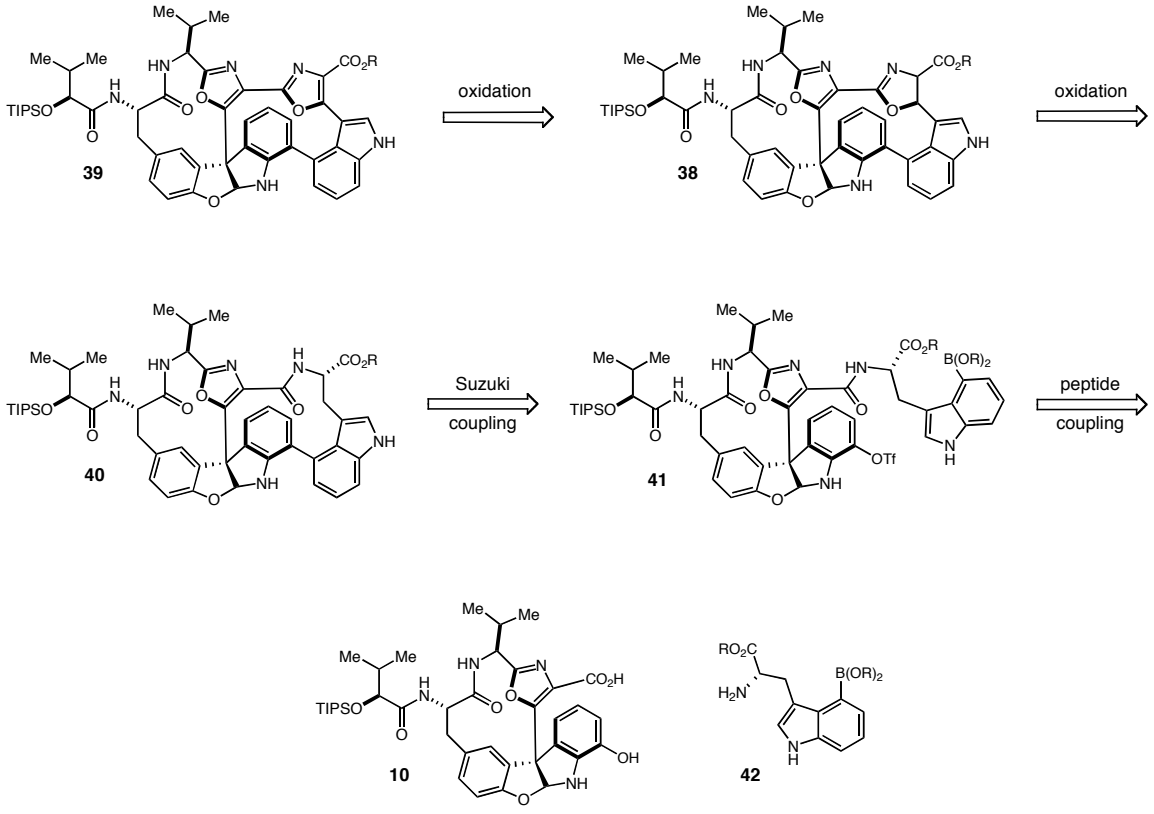
Figure 11: Retrosynthetic plan to dehydrogenate 4-acyloxazoline



excised at a later stage through any one of a variety of standard synthetic protocols. While this would necessitate a longer synthetic sequence, we felt the likelihood of success more than justified the added steps.

For this strategy to be carried out successfully, we would need to access an oxazoline substrate such as **38**. This was foreseen to arise retrosynthetically from a substrate **40**, which we reasoned should undergo oxidative ring contraction upon treatment with DDQ in a similar fashion to **22**, discussed previously (Figure 12). To create **40** we planned to utilize the peptide coupling/Suzuki macrocyclization sequence that had worked admirably in our earlier efforts. Retrosynthetically this prescribed coupling carboxylic acid **10** to a tryptophan derivate similar to **42**.

Figure 12: Retrosynthesis with acyloxazoline oxidation as a method to form the B-ring oxazole

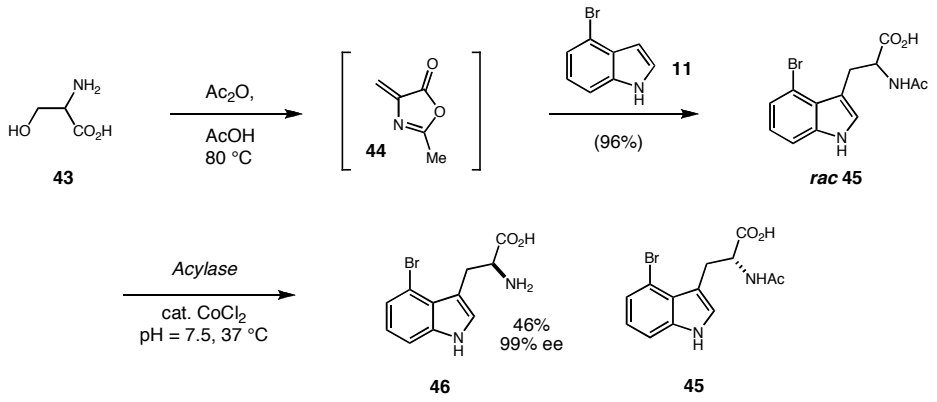


The synthesis of a functionalized tryptophan **42** was a somewhat more complex proposition than the previously described tryptamine syntheses had been, as the necessary amino acid stereocenter would have to be produced in a highly enantioenriched form to avoid the production of diastereomers when coupled to enantiopure **10**. Yet, we felt that this problem was solvable and well worth investigating given the potential downstream reward. As such we set out with an initial goal to develop a concise, asymmetric synthesis of a suitably protected version of **42**.

Our synthetic investigations began with an attempt to adopt a known enzymatic resolution of racemic acyltryptophans to our current purpose. Using a modification of the method originally reported by Snyder, we alkylated serine with 4-bromoindole **11** in a mixture of AcOH and Ac_2O to provide racemic *N*-acyl tryptophan **45** in 96% yield

(Scheme 5).[10] This adduct was then subjected to the enzyme *Acylase* according to the procedure of Yokoyama, which effectively resolved the enantiomers of **45**, providing 46% of the (*L*)-configured, freebased amino acid **46** in 99% ee.[11] However, while this reaction was highly selective and easily carried out, the purification of the polar amino acid products away from the enzyme residue proved untenable on multigram scale, despite considerable efforts, and this method of producing **46** was subsequently abandoned. However, as an interesting aside, we found that the enzyme tolerated both benzyl and PMB protecting groups on the indole nitrogen of the resolution substrates without loss of efficiency or selectivity.[12]

Scheme 5: Enzymatic resolution route to enantiopure 4-bromotryptphan derivatives



Faced with this setback, we next elected to make use of a technology that had recently been developed in our laboratories by Dr. Muriel Amatore for the production of enantioenriched α-chloroaldehydes.[13] This methodology utilizes imidazolidinone catalyst

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[10] Snyder, H. R.; MacDonald, J. A. *J. Am. Chem. Soc.* **1957**, *79*, 1257–1259.

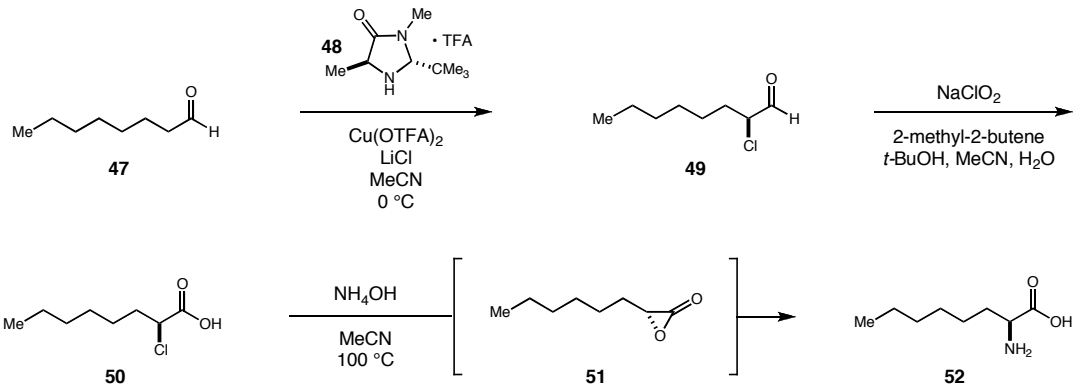
[11] Yokoyama, Y.; Hikawa, H.; Mitsuhashi, M.; Uyama, A.; Hiroki, Y., Murakami, Y. *Eur. J. Org. Chem.* **2004**, 1244–1253.

[12] For use of *acylase* enzymes in resoling a wide variety of unnatural *N*-acyl amino acids, see: Chenault, H. K.; Dahmer, J.; Whitesides, G. M. *J. Am. Chem. Soc.* **1989***, 111*, 6354–6364.

[13] Amatore, M.; MacMillan, D. W. C. *Unpublished results.*

48, which in conjunction with LiCl and a copper(II)trifluoroacetate oxidant, effects a highly efficient and uniformly enantioselective α-chlorination across a wide range of aldehyde substrates (Scheme 6). Furthermore, prior work in the MacMillan lab had shown that the conversion of these chloroaldehydes into their corresponding amino acids with net stereochemical retention and without loss of optical purity was easily accomplished in a simple three-step, one-pot protocol. We felt that this would be a particularly straightforward entry into the catalytic asymmetric synthesis of 4-bromotryptophans such as **42** and a forceful demonstration of this newly developed and valuable technique for the *de novo* synthesis of unnatural amino acids.[14]

Scheme 6: Asymmetric, organocatalytic synthesis of amino acids from chloroaldehydes

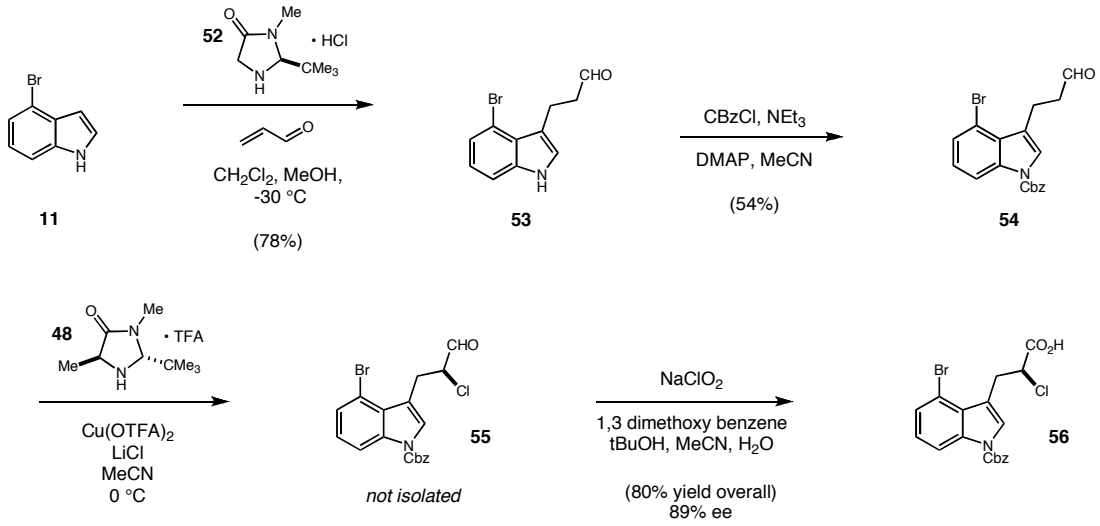


Toward this end, we set out to make the β-indolyl aldehyde substrate required for the proposed chlorination procedure. This was accomplished first by an iminium-catalyzed Friedel-Crafts addition of 4-bromoindole **11** into acrolein, giving product **53** in 78% yield (Scheme 7). The indole nitrogen of **53** was next acylated with CbzCl, yielding the substrate for our organocatalytic α-chlorination (**54**) in a scalable two-step sequence. Aldehyde **54** was then treated with *trans t*-butyl, methyl imidazolidinone catalyst **48**,

[14] Hong, J. B.; Jones, C. M.; Garcia-Garcia, P.; MacMillan, D. W. C. *Unpublished results.*

LiCl, and copper(II)trifluoroacetate in acetonitrile at room temperature to produce the desired chloroaldehyde **55**, which underwent *in situ* Pinnick oxidation to yield chloroacid **56** in 80% yield and 89% ee. Notably, 2-methyl-2-butene, which is frequently used as an *in situ* quench for the electrophilic HOCl byproduct generated during the reaction, was not nucleophilic enough to kinetically outcompete an undesired electrophilic chlorination of the indole ring. However, using the 1,3-dimethoxybenzene as hypochlorite scavenger prevents this undesired reaction pathway and allows the desired chloroacid to be produced cleanly and in high yield.

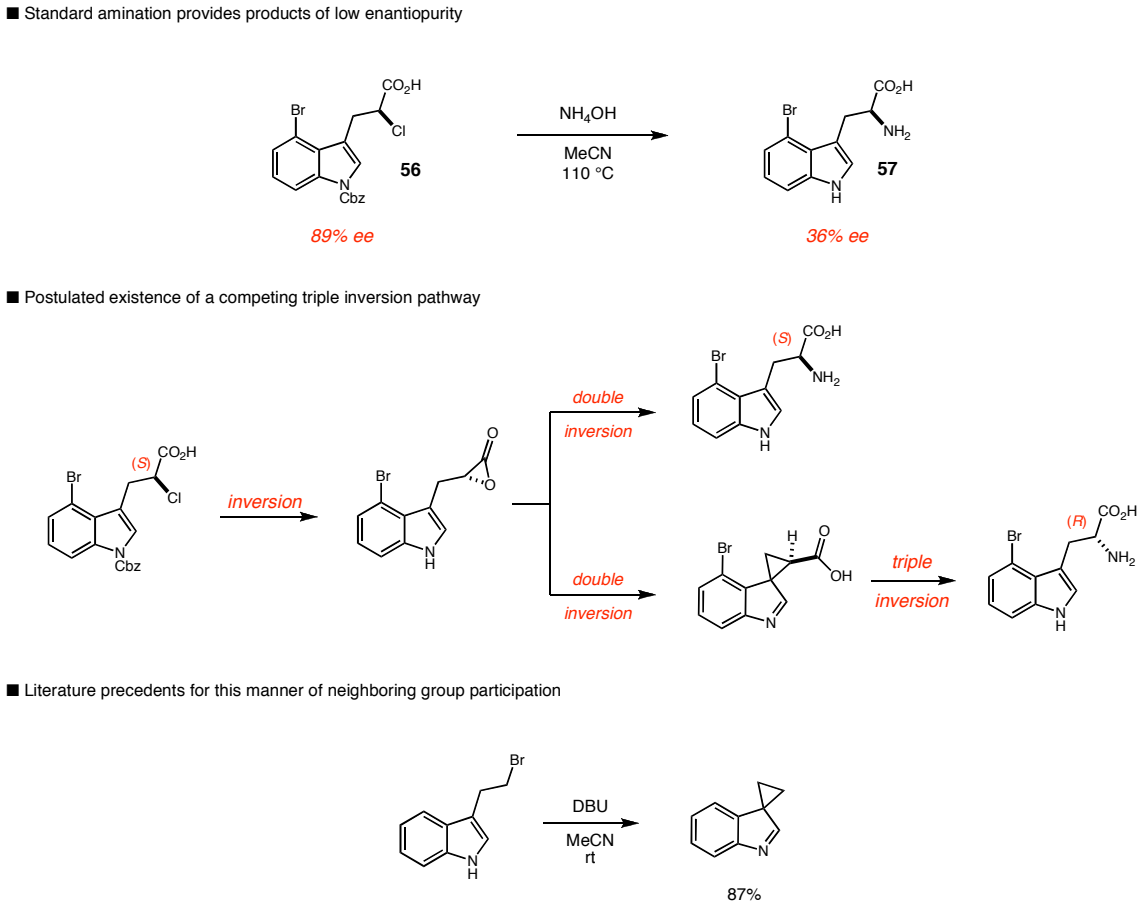
Scheme 7: Asymmetric, organocatalytic synthesis of enantioenriched α–chloroacid



However, when chloroacid **56** was subjected to the standard conditions developed for amination, the product was obtained in only 36% ee (Figure 13). We reasoned that this was likely due to the involvement of neighboring group participation from the indole ring in the displacement of the chloride. The proposed stereoretentive mechanism for these reactions is proposed to occur through initial intramolecular S_N2 attack of the carboxylic acid moiety on the adjacent chloride to yield a stereoinverted epoxylactone

intermediate, as shown in Figure 13. This epoxylactone is then opened and inverted again by ammonia to yield an amino acid product with the same configuration as the starting chloroacid. However, it is well known that electron-rich aromatics such as indoles are capable of displacing β-leaving groups, through the intermediacy of phenonium-type intermediates.[15] If this were to occur at an appreciable rate with substrate **56** it could create a possible triple inversion pathway to compete with the desired double inversion mechanism. The products of this new pathway would have a configuration opposite to that of the starting material, diminishing the enantiomeric purity of the product.

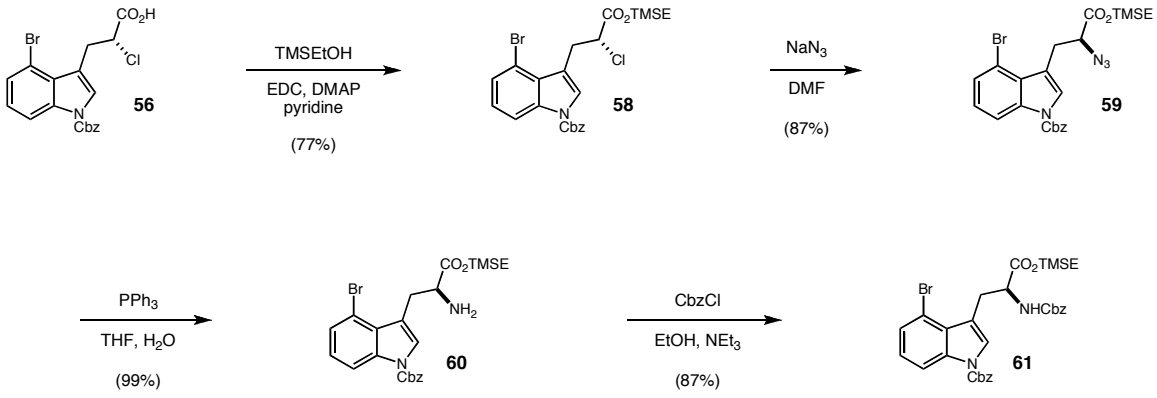
Figure 13: Initial attempts at amination of chloroacid



[15] Arumugam, S.; Verkade, J. G. *J. Org. Chem.* **1997**, *62*, 4287–4828.

To bypass this problem we employed an alternate, though less direct, method for the conversion of α-chloroaldehydes to amino acids reported by Jørgenson and coworkers.[16] The antipode of chloroacid **56** was synthesized in the previously described manner and was then coupled to trimethylsilylethanol to generate TMSE ester **58** in 77% yield (Scheme 8). The chloride was then displaced by sodium azide in DMF to yield the

Scheme 8: Revised attempt at amination of chloroacid



stereoinverted α-azidoester **59** in 87% yield. The azide product was then reduced with PPh_3 in aqueous THF at 50 °C to yield the amine product **60**, which was subsequently acylated as its benzyl carbamate, **61**. Notably, the enantiomeric excess of the starting material was retained throughout this sequence, giving fully protected tryptophan derivative **61** in a scalable and selective four-step sequence from **56**.

The aryl bromide was then transformed by a palladium-catalyzed Suzuki-Miyaura borylation to boronic ester **62** in 68% yield (Scheme 9). The benzyl carbamates of adduct **62** were reductively removed to yield the desired 4-boronic ester tryptophan **63**. Notably, none of the boronic ester functionality was reduced in this hydrogenolysis event.

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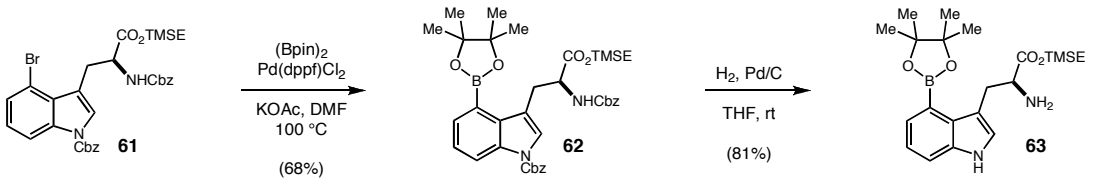
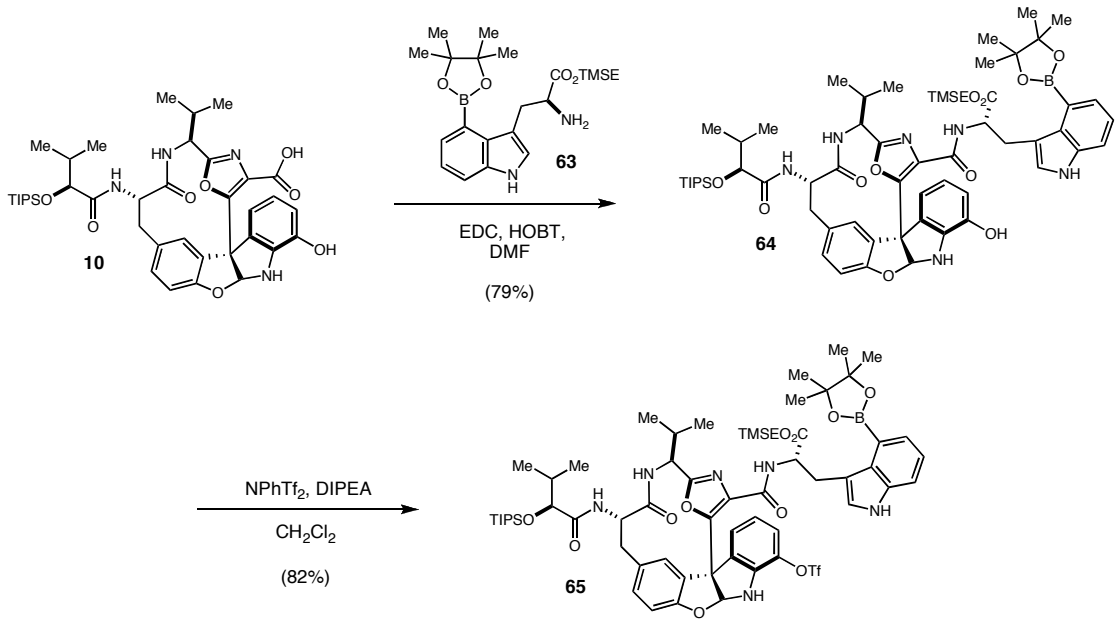
[16] Halland, N.; Braunton, A.; Bachmann, S.; Marigo, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 4790–4791.

Scheme 9: Completion of 4-boronic ester tryptophan synthesis



Amino ester **63** was next coupled to carboxylic acid **10** using EDC and HOBT in DMF to yield the product **64** in 79% yield (Scheme 10). This was followed by triflation of the phenol functionality, providing the substrate **65** for our key intramolecular Suzuki macrocyclization.

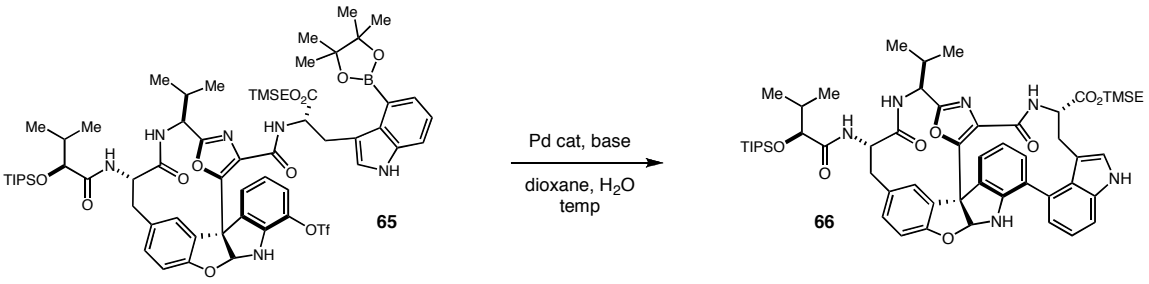
Scheme 10: Synthesis of third-generation Suzuki macrocyclization precursor



Gratifyingly, subjection of **65** to our standard Suzuki conditions successfully forged the desired the biaryl bond and the 13-membered macrocycle **66** in 52% yield (Table 2, entry 1). Yet, the yield of this process was still modest and for the sake of efficient material throughput we sought to improve upon it further. Given the specific dependence of reaction outcome on the catalyst, base, and solvent composition, we felt

that modulation of the reaction temperature was the most straightforward variable to investigate. However, we were wary that excessive heating under the basic reaction conditions presented a significant risk of epimerizing the amino acid-derived stereocenters. Fortunately, we observed raising the temperature to 100 °C afforded a modest increase in reaction efficiency with no observable epimerization (Table 2, entry 2). While the boiling point for the dioxane and water solvent system we employed was roughly 105 °C, carrying out these reactions under microwave irradiation allowed us to access substantially higher reaction temperatures, prompting us to investigate the observed dependence of efficiency on reaction temperature more fully.

Table 2: Third-generation Suzuki macrocyclization



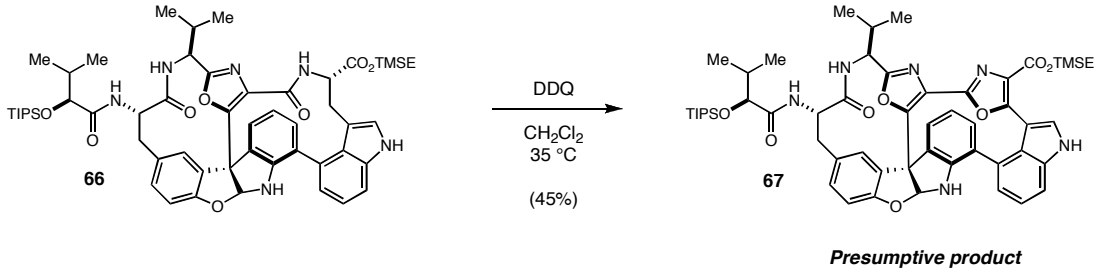
Entry	Pd Source	Base	Heating	Temp (°C)	Yield
1	$Pd(PPh_3)_4$	K_3PO_4	thermal	90	52%
2	$Pd(PPh_3)_4$	K_3PO_4	thermal	100	58%
3	$Pd(PPh_3)_4$	K_3PO_4	microwave	110	63%
4	$Pd(PPh_3)_4$	K_3PO_4	microwave	120	70%
5	$Pd(PPh_3)_4$	K_3PO_4	microwave	130	45%

Agreeably, we found that running the reactions at 110 °C in the microwave reactor provided the desired product **66** in an improved 63% isolated yield (Table 2, entry 3). Raising the temperature yet again to 120 °C provided the desired adduct in a satisfying 70% isolated yield (Table 2, entry 4) with no observable epimerization.

Notably, going to yet higher temperatures resulted in a lower overall reaction efficiency due to partial decomposition of the starting material (Table 2, entry 5). But we were pleased with these results nonetheless, as they represented one of the most efficient closures of the right-hand macrocycle in the diazonamide literature and provided material to investigate the subsequent ring contraction-oxidation strategy.

Biaryl **66** was subjected to DDQ in anhydrous THF in accordance with our previously described oxazoline formation. However, the presence of the electron-withdrawing β-ester required heating the reaction temperature to 80 °C in dioxane to effect the desired oxidation. Yet remarkably, along with the expected oxazoline was formed a small amount of what initially appeared by NMR and HRMS to be fully oxidized acyloxazole product **67** (Figure 14). Our strategy appeared to be even more effective than we anticipated as the ester group, while slowing the rate of the first oxidation, fully enabled the second in accord with our mechanistic hypothesis. Optimization of reaction conditions found that the desired reaction could be carried out with an excess of DDQ in CH_2Cl_2 at 35 °C to provide nominal **67** as the exclusive product in 45% isolated yield.

Figure 14: Presumptive direct oxidative installation of B-ring oxazole

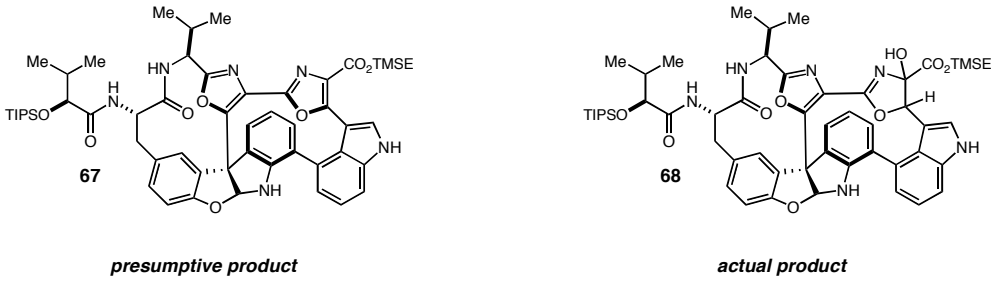


Presumptive product

However, one feature of the ^1H NMR was inconsistent with the structure of **67**, despite the accordance of the observed mass spectral data. Namely, there was a sharp

doublet resonance at 5.03 ppm that possessed a very small J-coupling to the proton at C(2) of C-ring indole and had a ^{13}C NMR resonance at 68.8 ppm. A battery of two-dimensional correlated NMR experiments finally revealed the true structure of **67** to be its corresponding hydrate **68** (Figure 15). Thus, we had indeed affected the desired double oxidation. However, the product was sufficiently reactive to irreversibly hydrate upon aqueous workup. We had been misled by initial mass spectroscopy of the isolated reaction product, as the nascent hydroxyl group eliminated readily upon ionization in the spectrometer, suggesting a desiccated form of the molecular ion with the molecular formula corresponding to a protonated form of **67**.

Figure 15: Identification of oxidation products



presumptive product ***actual product***

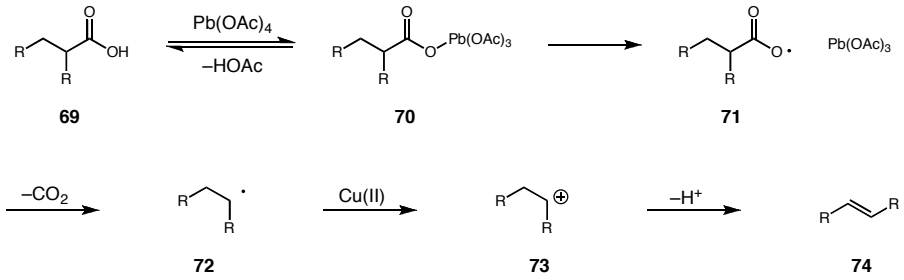
Unfortunately, all attempts to advance **68** met with failure. Treatment under even mildly basic conditions rapidly decomposed the starting material. Indeed, even attempts to deprotect the TMSE ester with TBAF or TASF caused immediate and non-productive consumption of the substrate. Notably, **68** was stable to treatment with acidic conditions, but still remained always in hydrated form upon isolation

Needless to say, given how close we had again come to success, this was easily our most disappointing setback. Our synthetic strategy had been effectively and succinctly reduced to practice, and our mechanistic insights had led to successful installation of the desired functionality in the desired manner. However, the instability of

the acyl oxazole moiety was a completely unforeseen, and seemingly unworkable, complication.

As such, we again set out to formulate an updated tactical approach. One particularly promising avenue considered was the oxidative decarboxylation of carboxylic acids. First described by J. K. Kochi, this rarely used reaction is a direct method of installing an unsaturation from a simple carboxylic acid precursor (Figure 16).[17] In a generalized mechanism, an acid (**69)** is treated with a metal oxidant, typically Pb(IV), Ce(IV), Mn(III), or Ag(I), which induces oxidation of the carboxylate to yield an oxygen-bound radical species (**71**). This intermediate then readily decomposes to expel carbon dioxide and yield a new alkyl radical **72**. This radical can then abstract a hydrogen atom from solvent or, in the presence of copper(II) salts, be oxidized to its corresponding carbocation **73**.[18] This cation can then intercept a solution nucleophile or eliminate to yield an olefinic product **74**.

Figure 16: Proposed mechanism of oxidative decarboxylation



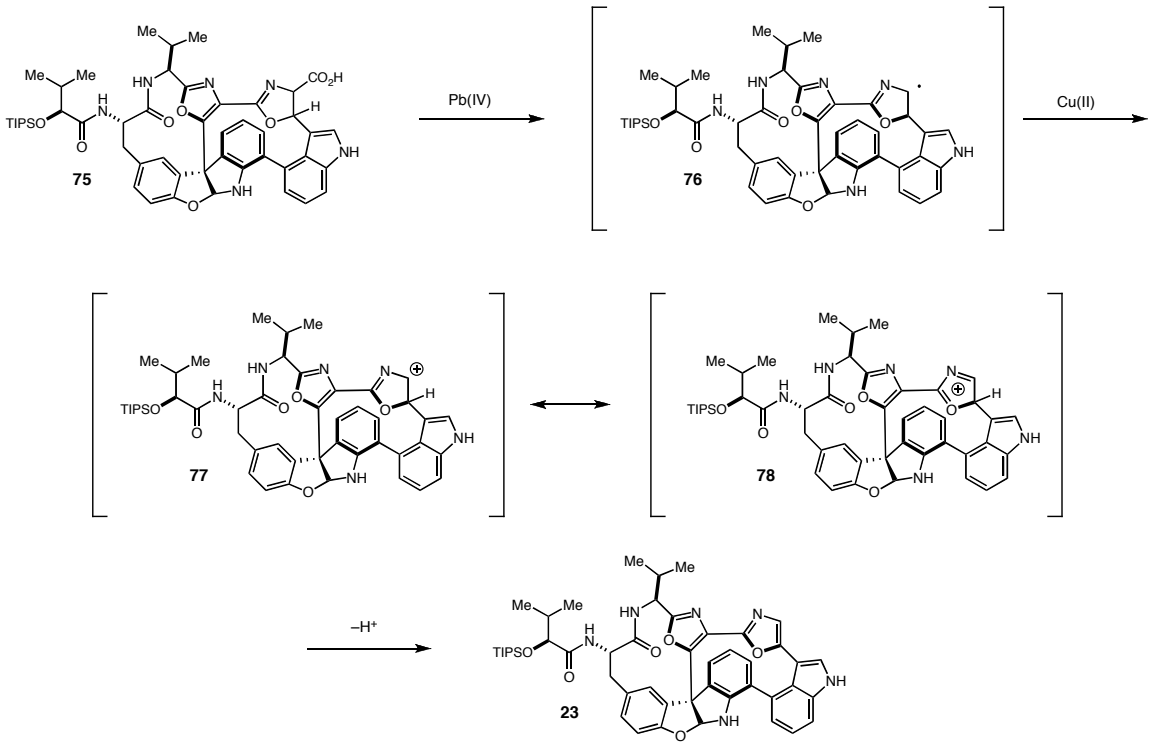
Application of this mechanistic scheme to our intermediate appeared promising. If anoxazoline acid such as **75** was treated under Kochi's Pb(IV)/Cu(II) conditions, it

[17] For lead references on oxidative decarboxylation, see: (a) Kochi, J. K.; Bacha, J. D.; Bethea, T. W. *J. Am. Chem. Soc.* **1967**, *89*, 6538–6547. (b) Bacha, J. D.; Kochi, J. K. *Tetrahedron*, **1968**, *24*, 2215–2226

[18] For lead references on the use of copper additives in oxidative decarboxylation see: Bacha, J. D.; Kochi, J. K. *J. Org. Chem*. **1968**, *33*, 2746–2754.

should result in the formation of a carboxyl radical which will fragment to yield radical **76** and CO_2 (Figure 17). This radical would then readily be oxidized by the copper(II) salts in solution to generate the carbocation **77**. Analysis of the resonance forms of this cation (**78**) reveals that it represents a protonated form of the oxazole, which should readily be deprotonated to return the desired aromatic product.[19]

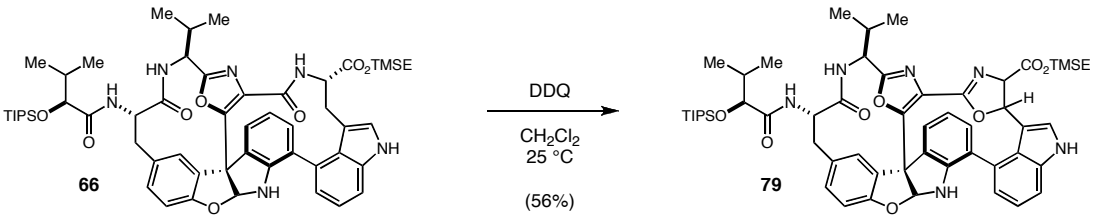
Figure 17: Retrosynthetic plan to carry out oxidative decarboxylation



Toward this end, we set our sights on the synthesis if oxazoline acid **75**. We knew from our previous investigations that we could generate the oxazoline ester by treating **66** with DDQ. In fact, the first oxidation was much faster than the second, allowing the oxazoline intermediate to be produced selectively. Optimization of the reaction times revealed conditions that produced the oxazoline **79** selectively in 56% yield (Figure 18).

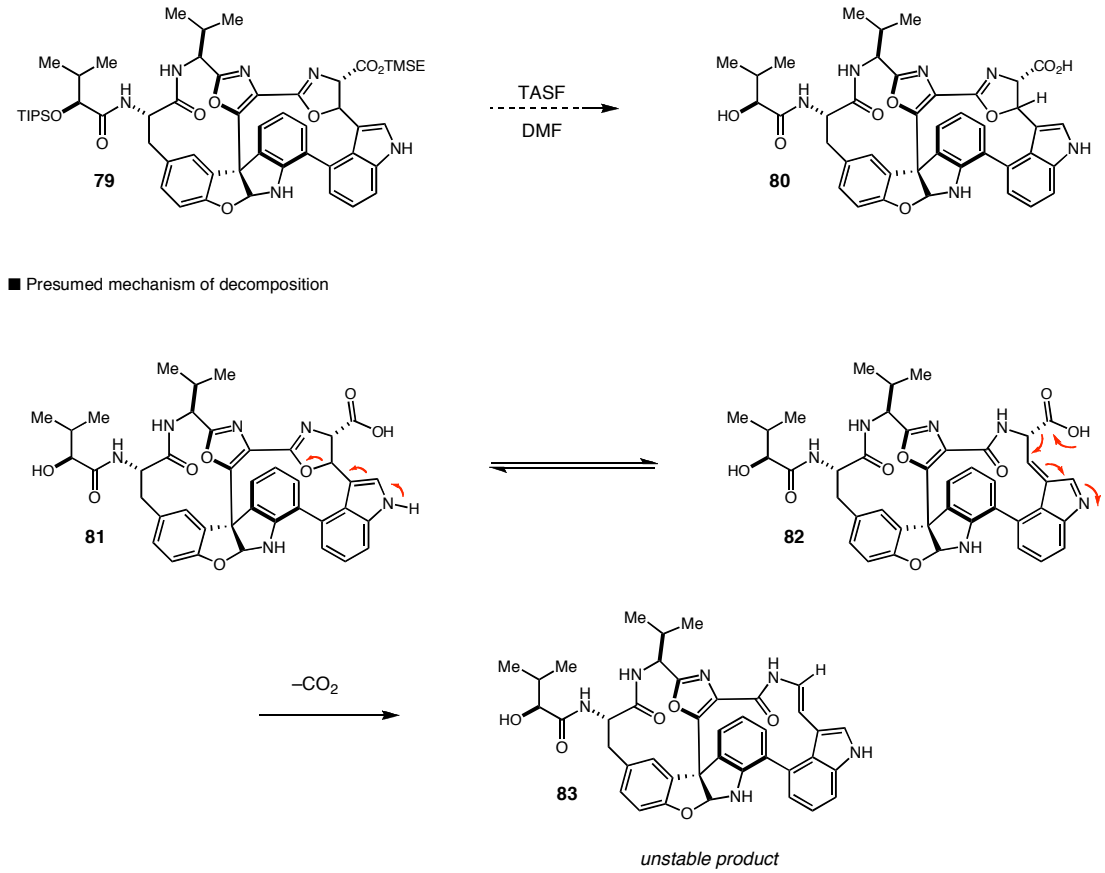
[19] For uses of oxidative decarboxylation in total synthesis, see: (a) Clive, D. J.; Minaruzzaman *Org. Lett.* **2007**, *9*, 5315–5317. (b) Padwa, A.; Brodney, M. A.; Lynch, S. M. *J. Org. Chem.* **2001**, *66*, 1716–1724. (c) Troast, D. M.; Porco, J. A. *Org. Lett.* **2002**, *4*, 991–994.

Figure 18: Oxidative installation of B-ring oxazoline



79 was then treated with TASF in DMF in an attempt to deprotect the TMSE ester (Figure 19). However, this resulted in formation of highly unstable reaction products that were much less polar than the expected carboxylic acid should have been. Mass spectral analysis of the crude reaction mixture exhibited ions that corresponded to loss of carbon

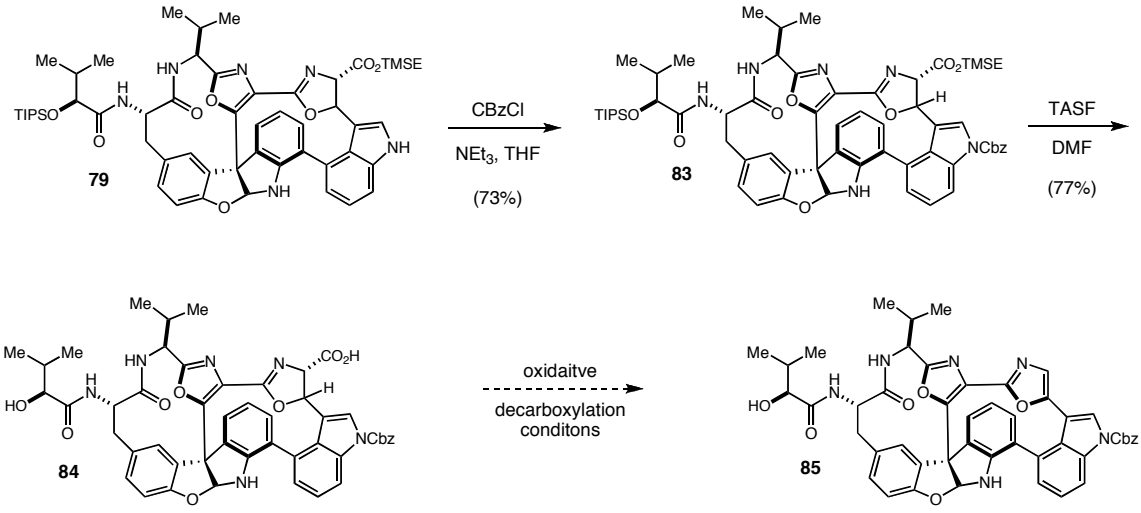
Figure 19: Initial failure to deprotect TMSE ester



dioxide from the starting material, and the crude NMR contained aldehydic methine resonances.

To account for these results, we surmised that the oxazoline ring was actually in equilibrium with an open form that arises from ring opening by attack of the adjacent electron-rich indole (Figure 19). With the ester group intact, this equilibrium was benign. Yet once the carboxylic acid is liberated, it is readily eliminated to quench the formal benzylic cation of the ring-opened isomer.[20] This presumably yields an unstable enamide product **82** that accounts for the crude reaction's mass spectral signals, and which, after undergoing aqueous workup, would be expected to produce aldehyde byproducts. The instability of the presumed adduct prevented this hypothesis from being rigorously demonstrated, but nonetheless it required us to alter our plans.

Figure 20: Successful deprotection of the TMSE ester



[20] For examples of the elimination of carboxylic acids with β-cations, see: (a) Cristol, S. J.; Norris, W. P. *J. Am. Chem. Soc.* **1953**, *75*, 632–636. (b) Grovenstein, E.; Lee, D. E. *J. Am. Chem. Soc.* **1952**, *74*, 2639–2644. (c) Cristol, S. J.; Norris, W. P. *J. Am. Chem. Soc.* **1953**, *75*, 2645–2646.

We reasoned that if this was indeed the source of the products instability, it should be possible to tone down the nucleophilicity of the adjacent ring by acylating the indole nitrogen. This was readily accomplished by treating ester **79** with CbzCl, DMAP and NEt_3 in THF to yield the acylated product **83** in 73% yield (Figure 20). This adduct was then treated with TASF in DMF, and, as we had predicted, acid **84** was isolated as a stable adduct.

However, all attempts to oxidatively decarboxylate **84** produced none of the desired bisoxazole product. Use of lead(IV) and silver(I) salts, with and without Cu(II) additives all met with similar results, with the starting material being consumed but with no identifiable products isolated. This approach still has potential due to wide variety of conditions known to affect this transformation, and is still an active area of investigation in the MacMillan lab.

IV. Conclusion and Future Direction

At the time of the writing of this thesis, efforts toward the synthesis of diazonamide A are ongoing in the MacMillan group. We feel certain that this strategy will ultimately prove successful, and that our current difficulties are primarily tactical in nature. Finding successful oxidative decarboxylation conditions should provide an adduct that can be easily advanced to the natural product. As such, investigating further oxidative decarboxylation conditions will hopefully yield the desired reaction outcome.

Chapter 5 Supporting Information

General Information: Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[21] All solvents were purified according to the method of Grubbs.[22] Nonaqueous reagents were transferred under argon via syringe or cannula. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator using a heated water bath. Chromatographic purification of products was accomplished using forced-flow chromatography on Silicycle 230–400 mesh silica gel 60 according to the method of Still.[23] Thin-layer chromatography (TLC) was performed on Silicycle 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by fluorescence quenching or by CAM stain.

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVANCE 500 (500 MHz and 125 MHz) as noted, and were internally referenced to residual solvent signals. Data for ^{1}H NMR were reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (Hz) and assignment. Data for ^{13}C NMR were reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer 1000 spectrometer and were reported in terms of frequency of absorption (cm^{-1}). Mass spectra were obtained from the Princeton Mass Spectral

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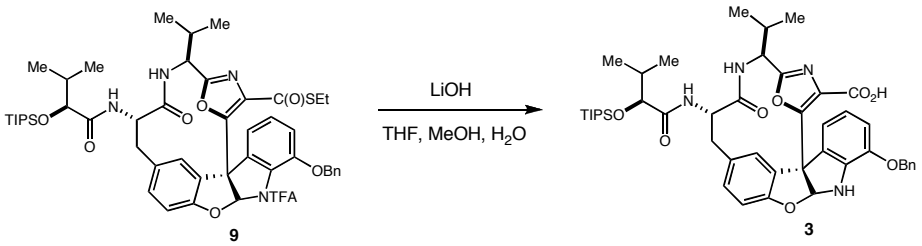
[21] Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals;* 3rd ed., Pergamon Press, Oxford, 1988.

[22] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.

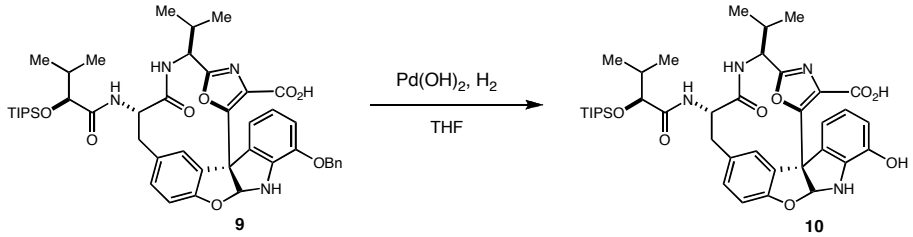
[23] Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978**, *43*, 2923.

Facility. Optical rotations were measured on a Jasco P-1010 polarimeter, and $[a]_D$ values were reported in 10^{-1} dg cm^2 g^{-1}.



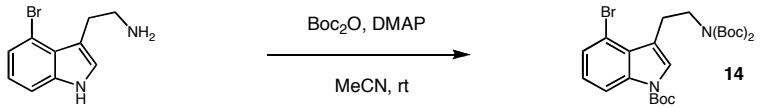
Acid 9: To a solution of **3** (84 mg, 0.087 mmol) in THF/MeOH/H_2O (4.4 mL, 10:2:1) was added LiOH•H_2O (36.5 mg, 0.87 mmol) with stirring. After the reaction was judged complete by TLC analysis (2 hours), the reaction mixture was diluted with 50 mL of diethyl ether, acidified with 1 N HCl to pH 2, and washed with 20 mL of brine. The organic portion was dried over sodium sulfate and concentrated *in vacuo*. These crude extracts were purified by column chromatography (50% EtOAc/Hexanes then 10% MeOH in CH_2Cl_2) to yield the title compound (71 mg, 99%) as a white amorphous solid. IR (Film): 3405, 2917, 2849, 1654, 1498, 1464, 1289, 1251, 1209, 1068, 882, 754, 684 cm^{-1}; ^{1}H NMR: (125 MHz, CD_3OD): δ 7.54–7.26 (m, 6H, Ar-**H**), 7.18 (dd, 1H, J = 8.2, 1.6 Hz, Ar-**H**), 6.94 (s, 1H, OC**H**N), 6.87–6.65 (m, 4H, Ar-**H**), 5.08 (s, 2H, OC**H**$_2$Ph), 4.93 (m, 1H, CONHC**H**CH), 4.53 (m, 1H, CONHC**H**CH_2), 4.16 (d, 1H, J = 3.9 Hz, C**H**OTIPS), 3.15 (t, 1H, J = 12.3 Hz, C**H**$_2$Ar), 2.85 (dd, 1H, J = 12.3, 3.8 Hz, C**H**$_2$Ar), 2.36 (m, 1H, NHCHC**H**$(CH_3)_2$), 2.05 (m, 1H, OCHC**H**$(CH_3)_2$), 1.09 (m, 24H, TIPS and NHCHCH(**C**$\mathbf{H_3}$)$_2$), 1.04–1.01 (m, 6H, NHCHCH(**C**$\mathbf{H_3}$)$_2$, OCHCH(**Me**)Me), 0.87 (d, 3H, J = 6.9 Hz, OCHCH(**Me**)Me); ^{13}C NMR: (75 MHz, CD_3OD) δ 172.7, 172.6, 165.9, 160.0, 157.2, 154.0, 144.0, 138.3, 137.0, 133.0, 130.6, 130.1, 130.0, 128.7, 128.2, 127.9,

127.6, 127.4, 127.3, 120.3, 114.9, 112.1, 110.2, 103.9, 70.2, 61.5, 55.6, 53.8, 38.6, 33.8, 28.6, 19.1, 17.6, 17.5, 17.1, 17.0, 16.6, 12.2; HRMS: (FAB+) exact mass calculated for [M+Na] ($C_{46}H_{58}N_4O_8SiNa$) requires *m/z* 845.3921, found *m/z* 845.3914; $[\alpha]_D^{25}$ = –100.66 (c = 0.493, $CHCl_3$).



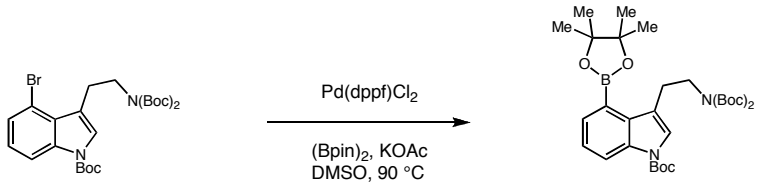
Phenol 10: To a solution of **9** (175 mg, 0.133 mmol) in THF (25 mL) was added $Pd(OH)_2/C$ (175 mg). The solution was sparged with H_2 for 20 minutes, heated to 40 °C and kept under a H_2 atmosphere for 4 hours. At this time the solution was filtered through a celite plug, concentrated, and the resulting solid was purified on silica gel (10% MeOH in CH_2Cl_2) to yield the title compound (150 mg, 100%) as a pale amorphous solid. IR (Film): 3406, 2962, 2868, 1652, 1601, 1493, 1414, 1295, 1251, 1184, 1097, 1063, 914, 882, 815, 758, 682 cm^{-1}; ^1H NMR: (125 MHz, CD_3OD): δ 7.52 (d, 1H, J = 8.7 Hz, Ar-**H**), 7.32 (s, 1H, Ar-**H**), 7.15 (dd, 1H, J = 8.4, 1.5 Hz, Ar-**H**), 7.02 (s, 1H, Ar-**H**), 6.78–6.54 (m, 4H, Ar-**H**, OC**H**N), 4.98 (m, 1H, CONHC**H**CH), 4.56 (m, 1H, CONHC**H**CH_2), 4.16 (d, 1H, J = 3.9 Hz, C**H**OTIPS), 3.15 (t, 1H, J = 12.0 Hz, C**H**$_2$Ar), 2.85 (dd, 1H, J = 12.3, 3.2 Hz, C**H**$_2$Ar), 2.40 (m, 1H, NHCHC**H**$(CH_3)_2$), 2.04 (m, 1H, OCHC**H**$(CH_3)_2$), 1.10 (m, 21H, TIPS), 1.02–0.98 (m, 9H, NHCHCH(**C**$\mathbf{H_3})_2$, OCHCH(**Me**)Me), 0.81 (d, 3H, J = 6.3 Hz, OCHCH(**Me**)Me); ^{13}C NMR: (75 MHz, CD_3OD) δ 172.8, 172.6, 171.6, 167.0, 159.8, 157.3, 153.2, 142.1, 137.0, 134.0, 131.2,

129.9, 129.8, 129.2, 127.8, 120.4, 114.7, 113.4, 110.0, 103.9, 78.0, 61.4, 60.1, 55.6, 53.7, 38.4, 33.8, 28.5, 18.8, 17.2, 17.1, 16.7, 16.3, 12.2; HRMS: (FAB+) exact mass calculated for [M+Na] ($C_{39}H_{52}N_4O_8SiNa$) requires *m/z* 755.3452, found *m/z* 755.3467; $[\alpha]_D^{25}$ = – 112.44 (c = 0.285, CH_3OH).



Boc tryptamine 14: To a solution of 6.4 g of 4-bromotryptamine (26.9 mmol) in 64 mL of dry MeCN was added 0.3 g of DMAP (2.69 mmol) followed by 18.2 g of Boc_2O (83.4 mmol). The resulting solution was heated to 40 °C and stirred under argon for 24 hours until it was judged by TLC that reaction progress had ceased. The solution was diluted with 100 mL of diethyl ether and 100 mL of saturated sodium bicarbonate solution. The layers were separated and the aqueous was washed with 2 x 100 mL of ether, and the combined organic was washed with 200 mL of brine. The solution was dried over sodium sulfate and concentrated to yield a black oil. At this point, the reaction was a nearly statistical and inseparable mixture of mono-, di-, and tri-Boc protected compound. Thus, the crude was resubjected to the reaction conditions described above once more until full conversion to the title compound had been achieved. Following workup as described above, the crude oil was chromatographed on silica gel (95:5 to 7:3 EtOAc:hexanes) to yield 8.6 g of the title compound in 60% yield as a viscous yellow oil. IR (Film): 3419 (br), 2980, 2934, 1789, 1738, 1698, 1422, 1368, 1282, 1256, 1140, 1112, 1024, 953, 852, 801, 778, 746 cm^{-1}; ^1H NMR: (125 MHz, $CDCl_3$) δ 8.15 (d, 1H, J = 8.4 Hz, C-7 Ar-H),

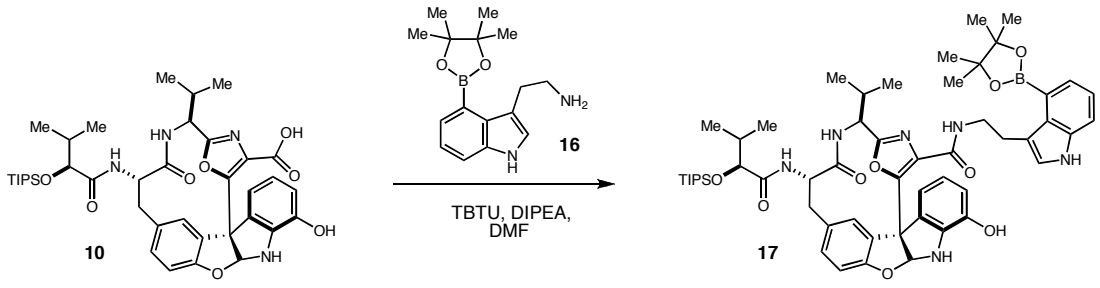
7.36 (dd, 1H, J = 0.9 Hz, 7.8 Hz, C-5 Ar-H), 7.35 (s, 1H, C-2 Ar-H), 7.093 (dd, 1H, J = 8.4 Hz, 7.8 Hz, C-6 Ar-H), 3.97 (t, 2H, J = 6.6 Hz, C**H$_2$**N), 3.22 (t, 2H, J = 6.6 Hz, ArC**H$_2$**), 1.63 (s, 9H, CMe_3), 1.36 (s, 18H, 2xCMe_3); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 152.7, 149.3, 128.8, 127.3, 125.7, 125.3, 118.2, 114.7, 114.5, 84.2, 82.2, 46.9, 41.2, 28.3, 28.2, 28.1, 25.9; HRMS (FAB+) exact mass calc. for [M+•] ($C_{25}H_{35}N_2O_6Br$) requires *m/z* 538.1678, found *m/z* 538.1683.



14 **15**

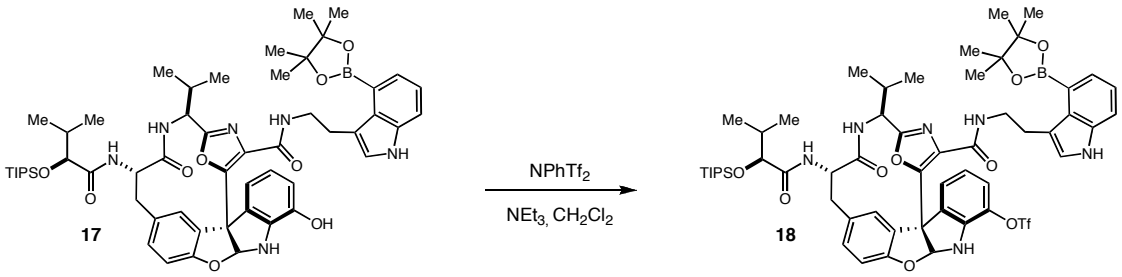
Boronic ester-tryptamine 15: Inside a glove box a 100 mL flask was charged with 3.1 g **14** (5.75 mmol), 0.47 g of $Pd(dppf)Cl_2$ (0.58 mmol), 2.92 g of $(Bpin)_2$ (11.5 mmol), and 2.26 g of KOAc (23.0 mmol). The flask was sealed with a rubber septa, purged of atmosphere, and was charged with 30 mL of DMSO via syringe under argon. The resulting solution was heated to 95 °C for 12 hours until judged complete by TLC. After cooling to room temperature, the reaction was diluted with 40 mL of diethyl ether and 40 mL of water, and the resulting black, biphasic solution was filtered through a celite pad to remove the insoluble solids. The pad was subsequently rinsed twice with 100 mL of ether. The resulting biphasic solution was separated, and the aqueous was washed 3 x 100 mL with ether, and the combined organic was washed with brine then dried over sodium sulfate. Following concentration, the resulting black oil was chromatographed on silica gel (95:5 to 9:1 EtOAc:hexanes) to yield 2.06 g the title compound as an off-white solid

in 67% yield. IR (Solid): 2979, 2933, 1785, 1732, 1698, 1600, 1455, 1415, 1368, 1282, 1137, 1047, 965, 898, 852, 765 cm^{-1}; ^{1}H NMR: (125 MHz, $CDCl_3$) δ 8.29 (d, 1H, J = 8.4 Hz, C-7 Ar-H), 7.68 (dd, 1H, J = 0.9 Hz, 6.9 Hz, C-5 Ar-H), 7.32 (s, 1H, C-2 Ar-H), 7.27 (m, 1H, C-6 Ar-H), 3.95 (t, 2H, J = 6.6 Hz, C**H**$_2$N), 3.21 (t, 2H, J = 6.6 Hz, ArC**H**$_2$), 1.63 (s, 9H, CMe_3), 1.37 (s, 12H, 4 x Me_3), 1.33 (s, 18H, 2 x CMe_3); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 152.8, 149.8, 135.9, 133.9, 131.1, 124.3, 84.1, 83.7, 83.5, 82.0, 46.1, 28.4, 28.1, 26.4, 25.2, 25.1; HRMS (FAB+) exact mass calc. for [M+•] ($C_{31}H_{47}N_2O_8B$) requires *m/z* 586.3425, found *m/z* 586.3437.



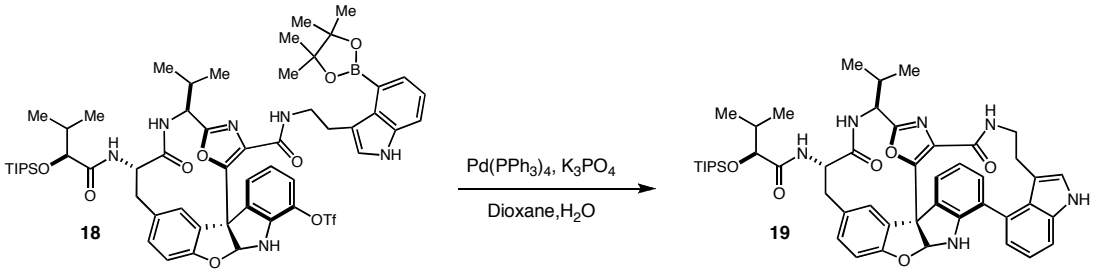
Boronic ester 17: A 25 mL flask was charged with 43 mg of **10** (0.0587 mmol), 40 mg of **16** (0.0881 mmol), and 20.7 mg of TBTU. The flask was sealed with a rubber septa and 5.9 mL of DMF was added by syringe under argon. To the resulting solution was added 31 μL of DIPEA (0.176 mmol) via syringe under argon and the reaction was stirred at room temperature for 12 hours until judged complete by TLC. The reaction mixture was then diluted in 100 mL of EtOAc and washed 2 x 50 mL with water and 2 x 50 mL with brine. The combined aqueous fractions were then back extracted with 2 x 50 mL of EtOAc. The combined organic layers were then washed once more with 100 mL of brine and dried over sodium sulfate. Following concentration, the crude solids were purified by

flash chromatography on silica gel (95:5 CH_2Cl_2:MeOH) to yield 54.4 mg (91%) the title compound as an off-white solid. IR (Film): 3402, 2962, 2929, 2868, 2360, 2341, 1652, 1600, 1506, 1371, 1295, 1143, 1135, 755, 684, 668 cm^{-1}; ^1H NMR: (300 MHz, CD_3OD) δ 7.64 (br m, 1H, NH), 7.55–7.48 (m, 3H, Ar-H and N-H), 7.38 (d, 1H, J = 1.8 Hz, Ar-H), 7.14 (dd, 1H, J = 1.8 Hz and 8.1 Hz, Ar-H), 7.06 (br s, 1H, N-H), 7.03 (m, 2H, Ar-H), 6.78 (dd, 1H, J = 3.4 Hz and 4.9 Hz, Ar-H), 6.76 (s, 1H, OC**H**NH), 6.62 (m, 2H, Ar-H), 4.93 (d, 1H, J = 6.6 Hz, C**H**N), 4.47 (m, 1H, C**H**N), 4.15 (d, 1H, J = 3.9 Hz, CHOTIPS), 3.45 (m, 2H, C**H₂**N), 3.24 (m, 3H, ArC**H₂**CH_2 and ArC**H**(H)CHN), 2.81 (m, 1H, ArCH(**H**)CHN), 2.23 (m, 1H, C**H**Me_2), 2.06 (m, 1H, C**H**Me_2), 1.34 (s, 12H, 4 x Me), 1.12 (m, 21H, TIPS), 1.10 (d, 1H, J = 3.4 Hz, CH**Me**(Me)), 1.07 (d, 1H, J = 6.7 Hz, CH**Me**(Me)), 1.02 (d, 1H, J = 7.0 Hz, CH**Me**(Me)), 0.91 (d, 1H, J = 6.7 Hz, CH**Me**(Me)); ^{13}C NMR: (75 MHz, CD_3OD) δ 172.60, 172.56, 161.0, 159.9, 157.2, 153.3, 142.3, 136.9, 136.7, 131.2, 130.2, 130.0, 128.8, 128.9, 127.9, 124.0, 120.4, 119.8, 114.9, 114.1, 113.3, 113.1, 110.0, 103.6, 83.4, 78.0, 61.4, 55.7, 53.4, 40.5, 38.3, 33.8, 28.6, 25.7, 23.92, 23.86, 18.8, 17.21, 17.17, 17.12, 16.7, 12.2; HRMS (FAB+) exact mass calc. for [M+H•] ($C_{55}H_{74}N_6O_9BSi$) requires *m/z* 1001.538, found *m/z* 1001.539; $[\alpha]_D^{25}$ = –38.7 (c = 0.2133, $CHCl_3$). *Nota bene:* Amine starting material **16** was prepared by dissolving protected amine **15** in neat TFA for five minutes then concentrating *in vacuo*. The resulting oil was reconcentrated 3 times from toluene to remove residual TFA. **16** was used in the reaction described above without further purification.



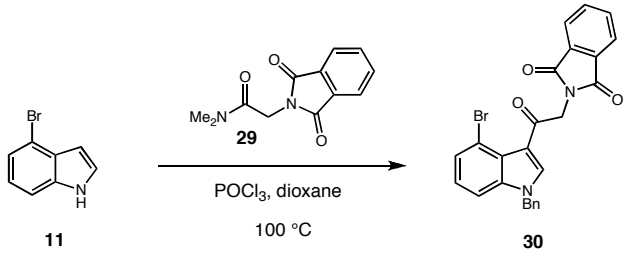
Aryl triflate 18: To a solution of 84 mg of **17** (0.084 mmol) in 8.4 mL of CH_2Cl_2 was added 73 μL of DIPEA (0.42 mmol) via syringe. To the resulting solution was added 90 mg of $NPhTf_2$ (0.25 mmol). The resulting solution was stirred at room temperature for 10 hours until judged complete by TLC. The crude reaction was then diluted with 100 mL of EtOAc and 100 mL of saturated $NaHCO_3$. The layers were separated and the aqueous was washed with 2 x 50 mL of EtOAc. The combined organic fractions were then washed with 100 mL of brine and dried over sodium sulfate. Following concentration, the crude solid was purified by flash chromatography on silica gel (97.5:2.5 CH_2Cl_2:MeOH) to yield 80 mg (84%) of the title compound as an off-white solid. IR (Film): 3406, 3287, 2963, 2933, 2360, 1652, 1496, 1423, 1210, 1140, 1062, 912, 882, 812, 755, 684 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ 8.05 (br d, 1H, J = 2.1 Hz Ar-H), 7.65 (dd, 1H, J = 1.2 Hz and 7.2 Hz, A-H), 7.51 (d, 1H, J = 2.1 Hz, Ar-H), 7.43 (dd, 1H, J = 1.2 Hz and 8.1 Hz, Ar-H), 7.17 (m, 3H, Ar-H), 7.10 (dd, 1H, J = 1.8 Hz and 8.7 Hz, Ar-H), 7.04 (dd, 1H, J = 0.9 Hz and 8.4 Hz, Ar-H), 7.00 (m, 1H, Ar-H), 6.75 (m, 2H, Ar-H), 5.94 (d, 1H J = 9.3 Hz, NH), 5.56 (d, 1H J = 4.2 Hz, NH), 5.05 (dd, 1H, J = 5.4 Hz and 9.3 Hz, C**H**N), 4.31 (m, 1H, C**H**N), 4.13 (d, 1H, J = 2.7 Hz, CHOTIPS), 3.55 (dd, 2H, J = 6.6 Hz and 9.9 Hz, C$\mathbf{H_2}$N), 3.35 (dd, 1H, J = 12 Hz and 12 Hz, ArC**H**(H)CHN), 3.18 (m, 2H, ArC$\mathbf{H_2}CH_2$), 2.73 (dd, 1H, J = 3.3 Hz and 12 Hz, ArC**H**(H)CHN), 2.29 (m, 1H, C**H**Me_2), 2.01 (m, 1H, C**H**Me_2), 1.35 (s, 12H, 4 x Me), 1.07 (m, 21H, TIPS), 1.02 (d, 3H, J = 6.9 Hz,

CH**Me**(Me)), 0.97 (d, 3H, J = 6.9 Hz, CH**Me**(Me)), 0.93 (d, 3H, J = 7.0 Hz, CH**Me**(Me)), 0.85 (d, 3H, J = 6.9 Hz, CH**Me**(Me)); ^{13}C NMR: (75 MHz, CD_3OD) δ 172.62, 172.56, 160.8, 160.7, 160.0, 157.3, 152.2, 141.3, 136.7, 133.2, 131.79, 131.76, 130.5, 129.84, 129.78, 129.0, 128.3, 128.0, 127.9, 126.1, 124.0, 122.5, 122.0, 120.9, 120.8, 119.9, 119.1, 116.5, 114.2, 113.2, 110.3, 103.4, 83.4, 78.0, 60.8, 55.6, 53.6, 40.6, 40.5, 38.3, 33.8, 28.8, 25.7, 23.93, 23.89, 18.7, 17.2, 17.1, 16.71, 16.69, 12.2; ^{19}F NMR: (75 MHz, $CDCl_3$) -75.84 (s, 3F, CF_3). HRMS (FAB+) exact mass calc. for [M+H•] ($C_{65}H_{75}N_6O_{11}BSSiF_3$) requires *m/z* 1135.503, found *m/z* 1135.502; $[\alpha]_D^{25} = -30.3$ (c = 0.36, $CHCl_3$).



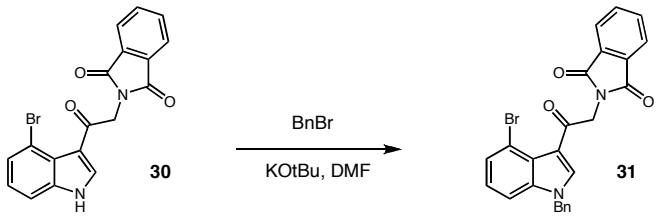
Biaryl 19: A Schlenk vial was charged with **18** (15 mg, 0.013 mmol), K_3PO_4 (5.5 mg, 0.0040 mmol) and $Pd(PPh_3)_4$ (4.6 mg, 0.0040 mmol). To this vial was added degassed dioxane/H_2O (5:1, 3.3 mL). The resulting solution was warmed to 70 °C for 5 hours. At this time the solution was diluted with EtOAc, and Na_2SO_4 was added to precipitate remaining palladium. This solution was filtered through florisil, concentrated, and the resulting oil was purified by prep TLC (100:25:4 CH_2Cl_2:Hexanes:MeOH) to yield the title compound (4.3 mg, 38%) as a pale amorphous solid. ^{1}H NMR: (300 MHz, CD_3OD): δ 10.56 (s, 1H, C=CN**H**), 8.66 (d, 1H, J = 7.8 Hz, Ar-**H**), 7.54 (d, 1H, J = 9.0 Hz, Ar-**H**), 7.41 (d, 1H, J = 8.1 Hz, Ar-**H**), 7.24–7.15 (m, 4H, Ar-**H**), 6.99 (d, 1H, J = 7.2 Hz, Ar-**H**),

6.90 (t, 1H, J = 7.5 Hz, Ar-**H**), 6.75 (d, 1H, J = 8.1 Hz, Ar-**H**), 6.20 (s, 1H, OC**H**N), 4.73 (m, 1H, CONHC**H**CH), 4.59 (m, 1H, CONHC**H**CH_2), 4.16 (d, 1H, J = 3.9 Hz, C**H**OTIPS), 4.04 (m, 1H, $CH_2C\mathbf{H}_2NHCO$), 3.23 (t, 1H, J = 12.0 Hz, C$\mathbf{H}_2$Ar), 2.85 (m, 2H, C$\mathbf{H}_2$Ar, $CH_2C\mathbf{H}_2NHCO$), 2.68 (m, 1H, NHCHC**H**$(CH_3)_2$), 2.08 (m, 2H, OCHC**H**$(CH_3)_2$, C$\mathbf{H}_2CH_2NHCO$), 1.86 (dd, 1H, J = 15.3, 6.0 Hz, C$\mathbf{H}_2CH_2NHCO$), 1.11 (m, 21H, TIPS), 1.05–0.98 (m, 9H, NHCHCH(**C$\mathbf{H_3}$)$_2$**, OCHCH(**Me**)Me), 0.91 (d, 3H, J = 6.6 Hz, OCHCH(**Me**)Me); HRMS: (FAB+) exact mass calc. for [M+Na] ($C_{49}H_{61}N_6O_6Si$) requires *m/z* 857.4422, found *m/z* 857.4397; $[\alpha]_D^{25} = -337.6$ (c = 0.387, $CHCl_3$).



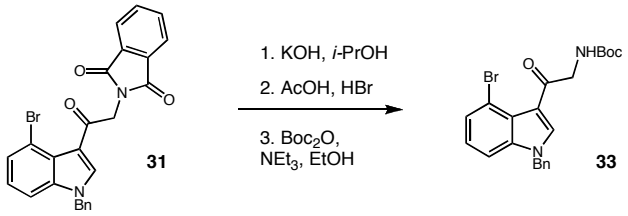
Ketone 30: To an oven-dried 100 mL flask with stirbar was added 4.20 g (18.10 mmol) of **29**. After being capped with a rubber septa, the flask was charged with 45 mL of dioxane introduced via syringe under argon. Next, 1.687 mL (18.10 mmol) of $POCl_3$ was added via syringe under argon. The flask was then fitted with a condenser, and heated to 95 °C under argon for one hour. The reaction mixture was then allowed to cool to room temperature. Next, 1.135 mL (9.05 mmol) of **11** was added via syringe through the septa on the condenser, and the resulting mixture was heated to reflux at 105 °C for 24 hours. After cooling to room temperature, 45 mL of water was added to the reaction mixture, followed by the dropwise addition of 1.0 M NaOH solution until the solution was pH 8. The resulting solution was heated to 100 °C for 20 minutes, then cooled in an ice bath.

The product precipitated as a light brown powder, which was then washed 3 x 100 mL with Et_2O and dried under vacuum for 24 hours to give 76% (2.65 g) of the title compound as a free-flowing tan powder. IR (Solid): 3312, 1769, 1704, 1673, 1657, 1513, 1426, 1396, 1317, 1314, 1200, 1143, 1100, 1087, 953, 777, 739 cm^{-1}; ^1H NMR: (500 MHz, d_6-DMSO) δ 12.49 (br s, 1H, N-H), 8.75 (s, 1H, C-2 Ar-H), 7.85–7.98 (m, 4H, phthalimide Ar-H), 7.54 (d, 1H, J = 8.1 Hz, C7 Ar-H), 7.40 (d, 1H, J = 8.1 Hz, J = 7.5 Hz, C-5 Ar-H), 7.15 (app t, 1H, J = 7.9 Hz, C-6 Ar-H) 5.08 (s, 1H, C**H₂**N); ^{13}C NMR: (125 MHz, $CDCl_3$) δ 184.6, 167.7, 138.7, 136.1, 134.7, 131.7, 127.1, 124.3, 124.2, 123.3, 113.7, 111.9, 45.3; HRMS (FAB+) exact mass calc. for [M+•] ($C_{18}H_{12}N_2O_3Br$) requires *m/z* 383.0031, found *m/z* 383.0048.



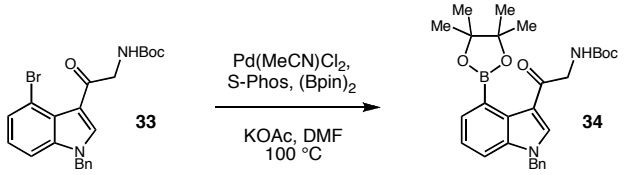
Ketone 31: To –40 °C solution of 1.96 g **30** (5.12 mmol) in 25 mL DMF under argon was added 603 mg of KOtBu (5.375 mol) in one portion. The resulting solution was stirred for 10 minutes, then 0.64 mL of benzyl bromide (5.21 mmol) was added via syringe under argon. The resulting solution was allowed to warm to room temperature over 2 hours. The crude mixture was diluted with 200 mL of EtOAc and 200 mL of pH 4 buffer. The layers were separated and the organic layer was washed with 100 mL of brine and dried over sodium sulfate. Following concentration, the crude mixture was purified by flash chromatography (2% acetone in CH_2Cl_2) to yield 1.68 g to title compound as a

white solid in 68% yield. IR (Film): 3112, 1766, 1710, 1676, 1604, 1557, 1524, 1419, 1389, 1317, 1212, 1192, 1105, 1067, 950, 907, 728, 713, 695 cm^{-1}; ^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.93 (s, 1H, C-2 ArH), 7.85 (m, 2H, N-Phth ArH), 7.72 (m, 2H, N-Phth ArH), 7.44 (d, 1H, J = 7.6 Hz, C-7 Ar-H), 7.32 (m, 3H, Bn Ar-H), 7.20 (d, 1H, J = 8.25 Hz, C-5 Ar-H), 7.12 (d, 1H, J = 6.5 Hz, Bn Ar-H), 7.04 (dd (apt t), 1H, J = 7.6 Hz, 8.25 Hz, C-6 Ar-H), 5.34 (s, 2H, C**H₂**N), 4.99 (s, 2H, C**H₂**Ar); ^{13}C NMR: (125 MHz, $CDCl_3$) δ 185.0, 168.1, 138.6, 135.5, 135.1, 134.0, 132.3, 129.3, 129.2, 129.04, 128.99, 128.5, 128.4, 126.9, 125.6, 124.6, 123.5, 123.4, 115.08, 114.99, 109.6, 51.1, 45.9; HRMS (FAB+) exact mass calc. for [M+•] ($C_{25}H_{16}N_2O_3Br$) requires *m/z* 473.0345, found *m/z* 473.0324.



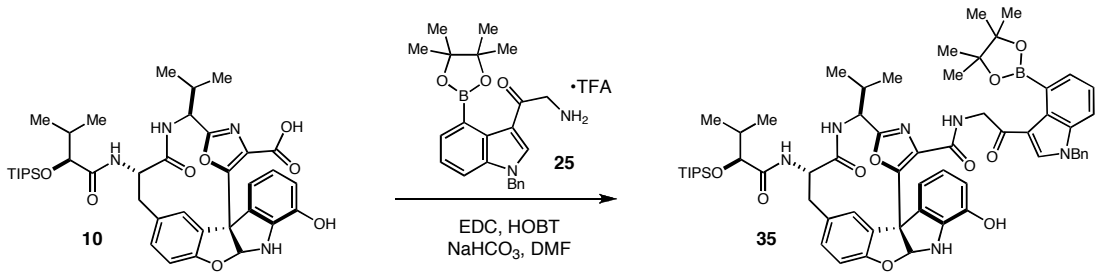
Aryl bromide 33: To a solution of bromide **31** (1.18 g, 2.46 mmol) in 50 mL of 4:1 a mixture of water and isopropanol was added 151 mg (2.71 mmol) of KOH pellets. The reaction was heated to 100 °C for three hours, then cooled to room temperature. The resulting solution was acidified to pH 4 with 10 M HCl and concentrated in vacuo. The resulting solids were then dissolved in 10 mL of water and 10 mL of 33% HBr in AcOH and the solution was heated to 75 °C for two hours. After cooling to room temperature the crude reaction mixture was concentrated and suspended in 100 mL of a 5:1 mixture of CH_2Cl_2 and hexanes. The suspension was filtered through a sintered glass frit, and the resulting solids were washed with 2 x 100 mL of a 5:1 mixture of CH_2Cl_2 and hexanes.

The resulting solid was then dissolved in 50 mL of ethanol and 1.24 mL of triethylamine (8.93 mmol) was added by syringe. 973 mg of solid Boc_2O was then added in a single portion and the resulting solution was stirred at room temperature for twelve hours. The crude mixture was concentrated, and the resulting oil was dissolved in 300 mL of EtOAc, to which was added 300 mL of water. The layers were separated and the organic was washed with 100 mL of saturated ammonium chloride and then 100 mL of brine, and then dried over sodium sulfate. This solution was then concentrated *in vacuo*, and purified by flash chromatography (1% MeOH in CH_2Cl_2) to yield 635 mg of the title compound as a tan solid, a total of 58% yield over the three-step sequence (unoptimized). IR (Film): 3417, 3331, 2976, 1709, 1675, 1555, 1522, 1497, 1454, 1434, 1392, 1365, 1275, 1259, 1167, 1067, 1024, 1045 cm^{-1}; ^1H NMR: (500 MHz, d_6-$CDCl_3$) δ 7.85 (s, 1H, Ar-H), 7.55 (d, 1H, J = 7.5 Hz, Ar-H), 7.39 (m, 2H, Ar-H), 7.33 (m, 2H, Ar-H), 7.16 (m, 3H, Ar-H), 5.68 (s, 1H, NH), 5.38 (s, 2H, CH_2Ar), 4.53 (d, 2H, J = 4.4 Hz, CH_2NH), 1.51 (s, 9H, CMe_3); ^{13}C NMR: (125 MHz, $CDCl_3$) δ 188.9, 155.9, 138.7, 135.0, 134.9 129.7, 128.6, 128.1, 127.1, 125.6 124.6, 124.5, 115.4, 115.0, 79.6, 51.0, 49.1, 28.4; HRMS (FAB+) exact mass calc. for [M+•] ($C_{22}H_{24}N_2O_3Br$) requires *m/z* 433.0970, found *m/z* 433.0991.



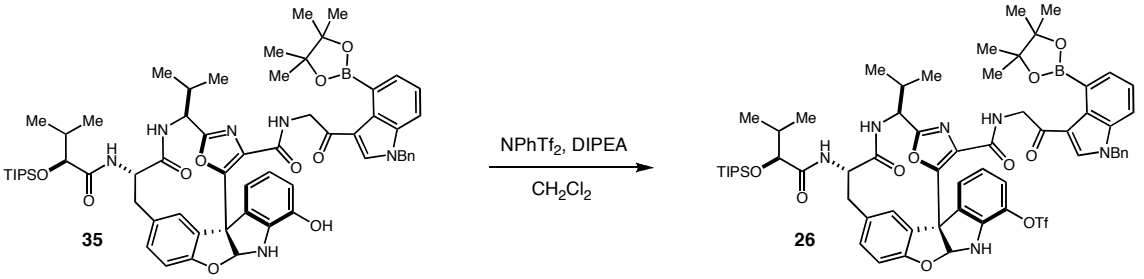
Boronic ester 34: Inside a glove box a 25 mL flask was charged with 300 mg of **33** (0.67 mmol), 8.76 mg of $Pd(MeCN)Cl_2$ (0.58 mmol), 41 mg of S-Phos (0.10155 mmol), 429

mg of $(Bpin)_2$ (1.69 mmol), and 265 mg of KOAc (2.708 mmol). The flask was sealed with a rubber septa, removed to atmosphere and charged with 6.8 mL of DMF via syringe under argon. The resulting solution was heated to 100 °C for 4 hours until judged complete by TLC. After cooling to room temperature, the reaction was poured into 100 mL of EtOAc and 100 mL of water, and the resulting black, biphasic solution was filtered through a celite pad to remove the insoluble solids. The pad was subsequently rinsed twice with 50 mL of EtOAc. The resulting biphasic solution was separated, and the aqueous was washed 3 x 50 mL with ethyl acetate, and the combined organic was washed with brine then dried over sodium sulfate. Following concentration, the resulting black oil was chromatographed on silica gel (35:65 to 1:1 EtOAc:hexanes) to yield 160 mg of the title compound as a white solid in 50% yield. IR (Film): 3421 (br), 2975, 2925, 1713, 1654, 1532, 1497, 1390, 1368, 1308, 1275, 1163, 1087, 852 cm^{-1}; ^1H NMR: (500 MHz, d6-$CDCl_3$) δ 7.76 (s, 1H, C-2 Ar-H), 7.42 (m, 1H, Ar-H), 7.34–7.26 (m, 6H, Ar-H), 7.33 (m, 2H, Ar-H), 7.09 (m, 1H, Ar-H), 5.51 (br m, 1H, NH), 5.33 (s, 2H, CH_2Ar), 4.45 (d, 2H, J = 6.0 Hz, CH_2N), 1.50 (s, 12H, 4 x Me), 1.47 (s, 9H, CMe_3); ^{13}C NMR: (125 MHz, $CDCl_3$) δ 188.5, 155.9 136.3, 135.4, 133.8, 129.1, 128.3, 127.8, 127.6, 127.0, 123.4, 115.0, 111.1, 83.9, 79.6, 50.8, 46.8, 28.4, 25.6; HRMS (FAB+) exact mass calc. for [M+H•] ($C_{28}H_{36}N_2O_5B$) requires *m/z* 491.2717, found *m/z* 491.2742.



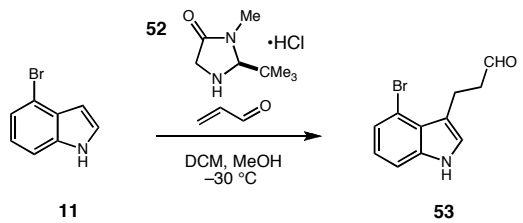
Phenol 35: A 10 mL flask was charged with **10** (23.85 mg, 0.0325 mmol, 1.0 eq), **25** (16 mg, 0.0325 mmol, 1.0 eq), EDC•HCl (7.5 mg, 0.039 mmol, 1.2 eq), HOBT (5.27 mg, 0.039 mmol, 1.2 eq), and $NaHCO_3$ (8.2 mg, 0.0977 mol, 3.0 eq). The flask was sealed with a rubber septa and 1.0 mL of DMF was added via syringe under argon. The resulting solution was stirred at room temperature for 4.5 hours and then poured into 100 mL of EtOAc. The resulting solution was washed with 2 x 100 mL of water and the aqueous fraction was back extracted with 100 mL of EtOAc. The resulting organic fraction was washed with brine, dried over sodium sulfate, and concentrated *in vacuo*. The resulting solids were purified by silica gel chromatography (1:1 EtOAc/hexanes) to yield the title compound (32 mg, 89%) as an off-white solid. IR (Film): 3405, 3291, 2964, 2936, 2865, 1656, 1600, 1513, 1389, 1297, 1180, 1140, 1092, 1067, 852, 753, 725 cm^{-1}; ^1H NMR: (400 MHz, $CDCl_3$) δ 8.135 (t, 1H, J = 4 Hz, Ar-H), 7.50 (d, 1H, J = 1.2 Hz, Ar-H), 7.40 (s, 1H, Ar-H), 7.27 (dd, 1H, J = 4.2 Hz and 9.0 Hz, Ar-H), 7.26 (m, 1H, Ar-H), 7.17 (m, 1H, Ar-H), 7.07 (m, 1H, Ar-H), 6.92 (s, 1H, C(10) CH), 6.88 (m, 1H, Ar-H), 6.68 (dd, 1H, J = 7.8 Hz and 13.6 Hz, Ar-H), 6.38 (dd, 1H, J = 8.0 Hz and 8.0 Hz, Ar-H), 6.24 (d, 1H, J = 8.0 Hz, Ar-H), 5.09 (m, 3H, PhC**H**$_2$ and C**H**NH), 4.52 (dd, 1H, J = 16 Hz and 4.4 Hz, ArCH(**H**)NH), 4.47 (m, 1H, C**H**NH), 4.37 (dd, 1H, J = 16 Hz and 4.4 Hz, ArCH(**H**)NH), 4.10 (d, 1H, J = 3.2 Hz, CHOTIPS), 3.34 (dd, 1H, J = 12 Hz and 12 Hz, ArC**H**(H)CHN), 2.74 (m, 1H, ArC**H**(H)CHN), 2.30 (m, 1H, C**H**Me$_2$), 1.99 (m, 1H,

C**H**Me_2), 1.47 (app d, 12H, J = 3.9 Hz, 4 x Me), 1.08 (br m, 24H, TIPS and CH**Me**), 0.96 (d, 3H, J = 6.9 Hz, CH**Me**), 0.92 (d, 3H, J = 6.9 Hz, CH**Me**), 0.87 (d, 3H, J = 6.9 Hz, CH**Me**); ^{13}C NMR: (125 MHz, $CDCl_3$) δ 186.8, 172.0, 160.9, 158.9, 157.3, 154.3, 141.8, 137.3, 135.9, 135.7, 135.1, 130.9, 130.8, 130.0, 128.8, 127.93, 127.90, 127.8, 127.6, 127.4, 126.5, 123.3, 121.1, 116.0, 113.9, 11.4, 110.6, 104.6, 83.8, 77.8, 61.4, 53.4, 50.75, 44.8, 38.8, 33.9, 29.1, 25.61, 25.57, 19.4, 18.2, 18.1, 18.0, 17.3, 17.1, 12.3; HRMS (FAB+) exact mass calc. for [M+H•] ($C_{62}H_{78}N_6O_{10}BSi$) requires *m/z* 1105.564, found *m/z* 1105.566; $[\alpha]_D^{25}$ = –47.7 (c = 1.225 $CHCl_3$). *Nota bene:* Amine starting material **25** was prepared by dissolving protected amine **34** in neat TFA for five minutes then concentrating *in vacuo*. The resulting oil was then reconcentrated 3 times from toluene to remove residual TFA. **25** was used in the reaction described above without further purification.



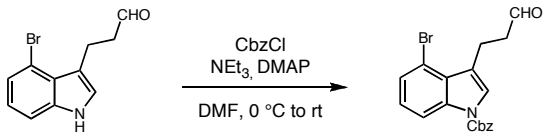
Triflate 35: To a solution of **26** (83 mg, 0.0752 mmol, 1.0 eq) in CH_2Cl_2 (3.76 mL) was added $PhNTf_2$ (36.7 mg, 0.0977 mmol, 1.3 eq) and Et_3N (31.5 µL, 0.225 mmol, 3.0 eq). The solution was stirred under argon for 4 hours and then diluted with saturated $NaHCO_3$. The aqueous layer was washed with EtOAc, and the combined organics were washed with H_2O and dried over Na_2SO_4. After concentration of the solvents *in vacuo*,

the resulting oil was purified on silica gel (1:1 EtOAc:hexanes) to yield the title compound (71 mg, 76%) as a pale off-white solid. IR (Film): 3402, 3289, 2962, 1657, 1514, 1496, 1423, 1389, 1211, 1140, 914, 882, 813 cm^{-1}; ^{1}H NMR: (300 MHz, $CDCl_3$) δ 8.05 (t, 1H, J = 4.2 Hz, Ar-H), 7.70 (s, 1H, Ar-H), 7.59 (d, 1H, J = 1.8 Hz, Ar-H), 7.40 (dd, 1H, J = 1.8 Hz and 3.0 Hz, Ar-H), 7.23 (m, 4H, Ar-H), 7.20 (d, 1H, J = 0.9 Hz, Ar-H), 7.10 (d, 1H, J = 4.5 Hz, Ar-H), 7.09 (dd, 1H J = 1.8 Hz and 8.1 Hz, Ar-H), 7.05 (m, 2H, Ar-H), 6.76 (d, 1H, J = 7.5 Hz, Ar-H), 6.67 (d, 1H, J = 8.1 Hz, Ar-H), 5.21 (app d, 2H, J = 6.6 Hz, C**H**$_2$Ph), 5.12 (m, 1H, C**H**NH), 4.58 (m, 2H, ArC**H**$_2$N), 4.42 (m, 1H, C**H**NH), 4.12 (d, 1H, J = 3.0 Hz, CHOTIPS), 3.40 (dd, 1H, J = 12 Hz and 12 Hz, ArCH(**H**)NH), 2.75 (dd, 1H, J = 3.3 Hz and 12 Hz, ArCH(**H**)NH), 2.33 (m, 1H, C**H**Me$_2$), 1.99 (m, 1H, C**H**Me$_2$), 1.50 (s, 12H, 4 x Me), 1.09 (m, 27H, TIPS and 2 x CH**Me**), 0.97 (d, 1H, 3.3 Hz, CH**Me**), 0.97 (d, 1H, 3.3 Hz, CH**Me**), 0.87 (d, 1H, 3.3 Hz, CH**Me**). ^{13}C NMR: (125 MHz, $CDCl_3$) δ 187.2, 171.9, 160.3, 159.2, 157.4, 152.3, 141.3, 136.2, 135.2, 134.2, 133.1, 133.0, 131.2, 130.45, 129.0, 128.3, 127.8, 127.6, 127.1, 127.0, 123.5, 122.4, 121.7, 120.2, 114.5, 111.1, 110.7, 103.5, 83.9, 78.0, 60.8, 53.2. 50.9, 45.3, 38.5, 33.9, 28.9, 25.6, 25.6, 19.4, 18.13, 18.09, 17.99, 17.4, 17.2, 12.4; HRMS (FAB+) exact mass calc. for [M+H•] ($C_{63}H_{77}N_6O_{12}BF_3SSi$) requires *m/z* 1237.513, found *m/z* 1257.516; $[\alpha]_D^{25}$ = –14.0 (c = 1.0 $CHCl_3$).



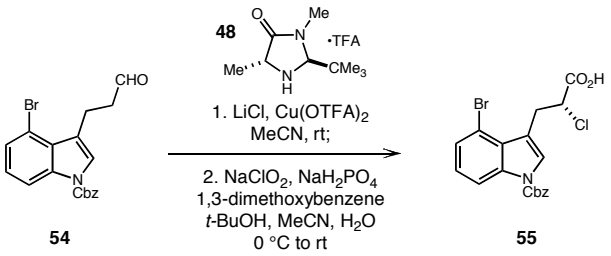
11 53

Aldehyde 53: To a –30 °C solution of 4-bromoindole **11** (5.0 g, 25.50 mmol) and imidazolidinone•HCl **52** (883 mg, 2.55 mmol) in 49 mL of CH_2Cl_2 and 2.55 mL of MeOH was added acrolein (0.852 mL, 12.75 mmol) dropwise in one portion. After 24 hours the reaction mixture was diluted with 300 mL of EtOAc washed with 2 x 100 mL saturated ammonium chloride solution. The organic portion was then washed with 200 mL of brine before being dried over sodium sulfate. The organic portion was concentrated *in vacuo*, and the resulting crude mixture was chromatographed in 15%–25% EtOAc in hexanes to afford 2.47 g (78%) of the title compound as a white, crystalline solid. IR (Film): 3417, 2926, 2830, 2728, 1714(s), 1614, 1548, 1424, 1335, 1185, 1082, 912, 802, 772, 737; ^{1}H NMR: (500 MHz, d_6-acetone) δ 10.38 (br s, 1H, N-H), 9.83 (s, 1H, CHO), 7.41 (d, 1H, J = 8.1 Hz, C-7 ArH), 7.27 (d, 1H, J = 2.1 C-2 ArH), 7.20 (app t, 1H, J = 7.85 Hz, C-5 ArH), 6.99 (dd, 1H, J = 7.5. 8.5 Hz, C-6 ArH), 3.32 (t, 2H, J = 7.4 Hz, Ar-CH_2), 2.87 (td, 2H, J = 7.4, 1.35 Hz, CH_2-CHO); ^{13}C NMR: (125 MHz, $CDCl_3$) δ 202.7, 139.3, 126.1, 125.5, 123.9, 123.3, 115.6, 114.2, 112.0, 46.3, 19.7; HRMS (ESI-TOF+) exact mass calc. for [M+•] ($C_{11}H_{10}NOBr$+Na) requires *m/z* 273.98435, found *m/z* 273.9843.



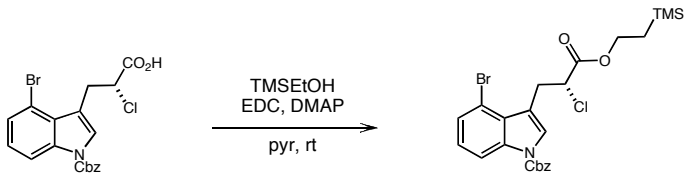
53 **54**

Aldehyde 54: To a 0 °C solution of aldehyde **53** (1.90 g, 7.5 mmol), triethylamine (4.2 mL, 30.1 mmol), and DMAP (924 mg, 7.5 mmol) in 40 mL of DMF was added CbzCl (3.22 mL, 22.6 mmol) dropwise over 15 minutes. The solution was allowed to warm to room temperature over 1.5 hours and was then diluted with 250 mL of EtOAc and 200 mL of saturated aqueous ammonium chloride. The layers were separated and the organic phase was washed with 2 x 200 mL of brine and then dried over sodium sulfate. Following concentration *in vacuo,* the crude extracts were purified by flash chromatography (20% EtOAc in hexanes) to afford the desired product as a colorless oil (1.34 g, 54%). IR (Film): 2819, 2722, 1730(s), 1602, 1557, 1424(s), 1391, 1356, 1248, 1181, 1096, 1053, 772, 758, 742, 698 cm^{-1}; ^{1}H NMR: (500 MHz, d_6-acetone) δ 9.82 (s, 1H, CHO), 8.22 (d, 1H, J = 8.25 Hz, C-7 ArH), 7.62 (s, 1H, C-2 ArH), 7.56 (app d, 2H, J = 7.15 Hz, Cbz-ArH), 7.42 (m, 4H, J = 7.15 Hz, C-5 ArH and Cbz-ArH), 7.22 (t, 1H, J = 8.0 Hz, C-6 ArH), 5.48 (s, 2H, $PhCH_2$), 3.26 (t, 2H, J = 7.4 Hz, C-7 $ArCH_2$), 2.90 (m, 2H, J = 7.4 Hz, CH_2CHO); ^{13}C NMR: (125 MHz, $CDCl_3$) δ 196.4, 150.9, 138.1, 136.4, 129.6, 129.51, 129.46, 129.1, 128.3, 126.6, 125.5, 121.5, 115.4, 114.6, 69.6, 44.9, 19.6; HRMS (ESI-TOF+) exact mass calc. for [M+•] ($C_{19}H_{16}NO_3Br$+Na) requires *m/z* 408.0211, found *m/z* 408.021.



Chloroacid 55: To a room temperature solution of imidazolidinone•TFA **48** (146 mg, 0.548 mmol), $Cu(OTFA)_2$ (2.38 g, 8.22 mmol), and LiCl (290 mg, 6.85 mmol) in 22 mL of MeCN was added the indole aldehyde **54** (1.06 g, 2.74 mmol) in one portion. The reaction was stirred at room temperature for 8 hours until judged complete by TLC. The reaction was diluted with 22 mL of *t*-BuOH and 13 mL of H_2O and cooled to 0 °C. NaH_2PO_4 (95 mg, 0.685 mmol) and 1,3-dimethoxybenzene (757 mg, 5.48 mmol) were added, followed by $NaClO_2$ (1.239 g, 13.7 mmol). The reaction was allowed to warm to room temperature over 1.5 hours until judged complete by TLC. The pH of the crude reaction was adjusted to 2 by the addition of 1 M HCl. Following extraction with 300 mL of EtOAc, the layers were separated and the organic layer was subsequently washed with 200 mL of brine and dried over sodium sulfate. Following concentration *in vacuo*, the crude extracts were purified by flash chromatography (80:20:1 hexanes:EtOAc:acetic acid) to yield the desired product as a white solid (0.954 g, 80%) in 88.5% enantiomeric excess. IR (Film): 3036, 1736, 1424, 1392, 1353, 1292, 1281, 1248, 1055, 910, 778, 742, 697; ^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.20 (br s, 1H, C-7 ArH), 7.58 (br s, 1H, C-2 ArH), 7.45 (app d, 2H, J = 6.75 Hz, Cbz-ArH), 7.41 (m, 4H, C-5 ArH and Cbz-ArH), 7.15 (t, 1H, J = 8.1 Hz, C-6 ArH), 5.42 (s, 2H, $PhCH_2O$), 4.75 (dd, 1H, J = 6.6 Hz and 7.9 Hz, CHCl), 3.77 (dd, 1H, J = 6.6 Hz and 14.8 Hz, ArCH), 3.40 (dd, 1H, J = 7.9 Hz and 14.8 Hz, ArCH); ^{13}C NMR: (125 MHz, $CDCl_3$) δ 195.54, 173.92, 134.65, 128.95, 128.87,

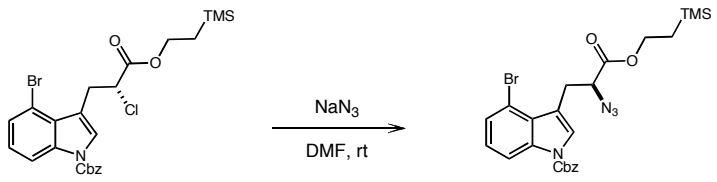
128.61, 127.75, 127.73, 126.89, 125.88, 115.49, 114.76, 113.68, 69.17, 56.24, 31.45l; HRMS (ESI-TOF+) exact mass calc. for [M+•] ($C_{19}H_{15}NO_4BrCl$+Na) requires *m/z* 457.9770, found *m/z* 457.9769; $[\alpha]_D$ = –15.14 (c = 1.0, $CHCl_3$) The enantiomeric purity of the title compound prepared determined by SFC analysis using a Chiracel ASH column (15% MeOH, 4mL/min): *R*-enantiomer: t_r = 5.02 min, *S*-enantiomer: t_r = 5.85 min.



56 **58**

Chloroester 58: To a room temperature solution of chloroacid **56** (954 mg, 2.188 mmol), trimethylsilylethanol (0.936 mL, 6.56 mmol), and DMAP (267 mg, 2.188 mmol) in 22 mL of pyridine was added EDC•HCl (838 mg, 4.376 mmol) in one portion. The reaction was stirred at room temperature for 20 hours until judged complete by TLC. The reaction was diluted with 300 mL of EtOAc and the resulting solution was washed with 3 x 150 mL 0.5 M HCl. The resulting organic layers was washed with 200 mL of brine and dried over sodium sulfate. Following concentration *in vacuo*, the crude extracts were purified by flash chromatography (9:1:1 hexanes:EtOAc:CH_2Cl_2) to yield the desired product as a clear oil (0.905 g, 77%). IR (Film): 3034, 2955, 2898, 1739 (s), 1602, 1558, 1424(s), 1392, 1351, 1248, 1161, 1092, 1054, 932, 858, 838, 777, 743, 697; ^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.20 (br s, 1H, C-7 ArH), 7.57 (s, 1H, C-2 ArH), 7.47 (m, 2H, Cbz-ArH), 7.42 (m, 4H, C-5 ArH and Cbz-ArH), 7.16 (t, 1H, J = 8.1 Hz, C-6 ArH), 5.44 (dd, 2H, J = 12.0

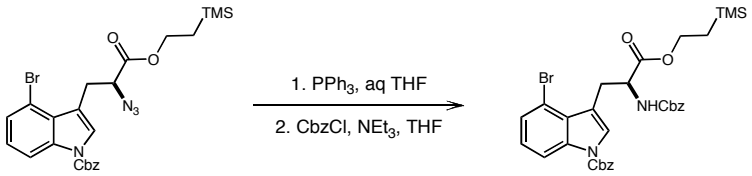
Hz and 16.0 Hz, $PhCH_2O$), 4.68 (t, 1H, J = 7.4 Hz, CHCl), 4.23 (m, 2H, CO_2CH_2), 3.70 (dd, 1H, J = 7.4 Hz and 14.7 Hz, ArCH), 3.45 (dd, 1H, J = 7.4 Hz and 14.7 Hz, ArCH), 0.95 (t, 2H, J = 7.5 Hz, CH_2TMS), 0.00 (s, 9H, TMS); ^{13}C NMR: (125 MHz, $CDCl_3$) δ 171.0, 151.7, 136.2, 130.5, 130.4, 129.4,129.3, 128.3, 127.3, 117.5, 116.2, 115.3, 70.6, 66.1, 58.1, 33.1, 18.6, 0.00. HRMS (ESI-TOF+) exact mass calc. for [M+•] ($C_{24}H_{27}NO_4BrClSi$+Na) requires *m/z* 558.04789, found *m/z* 558.0478; $[\alpha]_D$ = –8.99 (c = 2.11, $CHCl_3$).



58 **59**

Azide 59: To a room temperature solution of chloroester **58** (888 mg, 1.656 mmol) in 33 mL of DMF was added sodium azide (215 mg, 3.31 mmol) in one portion. The reaction was stirred at room temperature for 16 hours until judged complete by TLC. The reaction was diluted with 300 mL of EtOAc and the resulting solution was washed with 3 x 150 mL saturated NH_4Cl solution. The resulting organic layer was washed with 200 mL of brine and dried over sodium sulfate. Following concentration *in vacuo*, the crude extracts were purified by flash chromatography (10% to 15% EtOAc in hexanes) to yield the desired product as a clear oil (0.777 g, 87%). IR (Film): 2956, 2105(s), 1739(s), 1425(s), 1392, 1355, 1249(s), 1182, 1094, 1054, 859, 838, 777, 744, 697; ^1H NMR: (500 MHz, $CDCl_3$) δ 8.22 (br s, 1H, C-7 ArH), 7.57 (s, 1H, C-2 ArH), 7.49 (m, 2H, Cbz-ArH), 7.42 (m, 4H, C-5 ArH and Cbz-ArH), 7.16 (t, 1H, J = 8.1 Hz, C-6 ArH), 5.44 (s, 2H, PhCH-

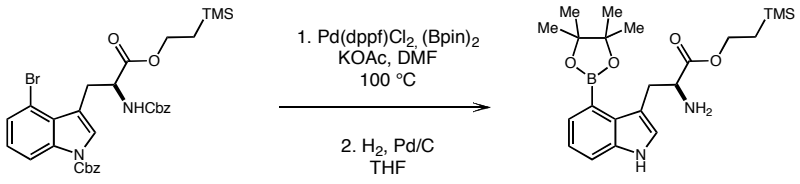
$_2$O), 4.33 (dd, 1H, J = 5.7, 8.9 Hz, CHN_3), 4.27 (m, 2H, CO_2CH_2), 3.64 (dd, 1H, J = 5.7 Hz and 14.8 Hz, ArCH), 3.20 (dd, 1H, J = 8.9 Hz and 14.8 Hz, ArCH), 0.99 (m, 2H, CH_2TMS), 0.00 (s, 9H, TMS); ^{13}C NMR: (125 MHz, $CDCl_3$) δ 171.7, 151.6, 136.3, 130.5, 130.4, 130.1, 129.4, 129.3, 127.8, 127.3, 117.6, 116.2, 115.4, 70.6, 66.0, 29.8, 18.9, 0.0; HRMS (EI +) exact mass calc. for [M+•] ($C_{24}H_{27}N_4O_4BrSi$+) requires *m/z* 542.0985, found *m/z* 542.0983; $[\alpha]_D$ = –6.45 (c = 1.0, $CHCl_3$).



59 **61**

Amino ester 61: To a room temperature solution of azide **59** (777 mg, 1.418 mmol) in 30 mL of a 5:1 THF/H_2O solution was added triphenylphosphine (450 mg, 1.715 mmol) in one portion. The reaction was heated to 50 °C and stirred for 3 hours until judged complete by TLC. The reaction was diluted with 300 mL of EtOAc and the resulting solution was washed with 150 mL saturated NH_4Cl solution. The resulting organic layer was washed with 200 mL of brine and dried over sodium sulfate. Following concentration *in vacuo*, the crude extracts were dissolved in 23 mL of THF and NEt_3 (1.0 mL, 7.09 mmol). The resulting solution was stirred and cooled to 0 °C before CbzCl (0.608 mL, 4.25 mmol) was added dropwise via syringe over 5 minutes. The reaction was stirred and allowed to warm to room temperature over 3 hours at which time it was judged complete by TLC. The reaction was diluted with 300 mL of EtOAc and the resulting solution was washed with 3 x 150 mL saturated $NaHCO_3$ solution. The resulting

organic layer was washed with 200 mL of brine and dried over sodium sulfate. Following concentration *in vacuo*, the crude extracts were purified by flash chromatography (10%–25% EtOAc in hexanes) to yield the desired product as a white solid (0.720 g, 78% over two steps). IR (Film): 3339, 2953, 1736, 1686, 1531, 1453, 1424, 1345, 1324, 1257, 1188, 1099, 1056, 971, 859, 835, 776, 760, 748, 730, 694 cm^{-1}; ^1H NMR: (500 MHz, $CDCl_3$) δ 8.21 (br s, 1H, C-7 ArH), 7.53 (s, 1H, C-2 ArH), 7.46 (m, 3H, ArH), 7.42–7.36 (m, 4H, ArH), 7.32–7.25 (m, 5H, ArH), 7.14 (t, 1H, J = 8.1 Hz, C-6 ArH), 5.41 (s, 2H, $PhCH_2O$), 5.03 (s, 2H, $PhCH_2O$), 4.79 (dt, 1H, J = 5.7, 8.9 Hz, CHNH), 4.18 (m, 2H, CO_2CH_2), 3.62 (dd, 1H, J = 5.7 Hz and 14.9 Hz, ArCH), 3.28 (dd, 1H, J = 8.6 Hz and 14.8 Hz, ArCH), 0.87 (m, 2H, CH_2TMS), 0.00 (s, 9H, TMS); ^{13}C NMR: (125 MHz, $CDCl_3$) δ 173.7, 157.3, 151.6, 138.5, 137.8, 136.2, 130.42, 130.37, 130.109, 130.03, 129.8, 129.67, 129.58, 129.4, 127.2, 118.3, 116.1, 115.7, 70.5, 68.4, 65.5, 56.3, 30.7, 18.7, 0.0; HRMS (ESI-TOF+) exact mass calc. for [M+H•] ($C_{32}H_{36}N_2O_6BrSi$+) requires *m/z* 651.1525, found *m/z* 651.1517; $[\alpha]_D = -2.3$ (c = 0.67, $CHCl_3$).

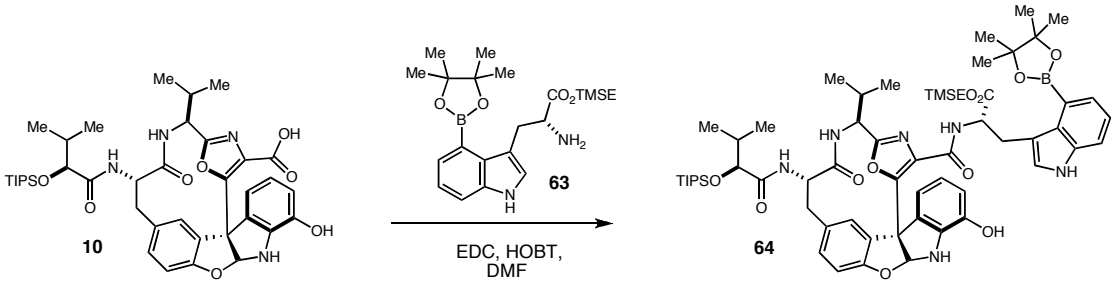


61 **63**

Boronic ester 63: A 25 mL flask was charged with 545 mg **61** (0.836 mmol), 68 mg of $Pd(dppf)Cl_2$ (0.0836 mmol), 531 mg of $(Bpin)_2$ (2.091 mmol), and 328 mg of KOAc (3.34 mmol) inside a glove box. The flask was sealed with a rubber septa, removed from the glove box, and charged with 5.6 mL of DMF via syringe under argon. The resulting

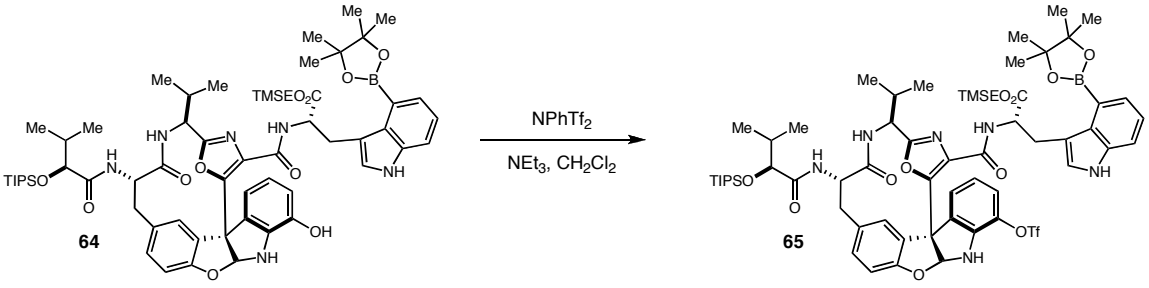
mixture was heated to 100 °C for 16 hours until judged complete by TLC. The solution was then cooled to room temperature, and then poured into 200 mL of EtOAc and 100 mL of brine. The layers were separated and the organic portion was washed with 2 x 100 mL saturated aqueous NH_4Cl and then 200 mL of brine. The resulting solution was filtered through a pad of florisil, dried over sodium sulfate, and concentrated. The boron byproducts and remaining $(Bpin)_2$ were removed by trituration of the resulting crude solids with 2 x 100 mL of pentane. Following this, the remaining solids were dissolved in 25 mL of THF and 325 mg of Pd/C is added in one portion. The solution was degassed under argon and then the flask was charged with one atmosphere of hydrogen gas. After stirring for 5 hours at room temperature the reaction was judged complete by TLC and filtered through a pad of celite. The celite pad was washed with 4 x 50 mL EtOAc and the resulting organic solution was concentrated *in vacuo*. The resulting crude solid was then purified by flash chromatography on silica gel (9:1 CH_2Cl_2:MeOH) to yield the title compound as a white solid (200 mg) in 55% yield over the two steps. IR (Film): 3384 (br), 3250 (br), 3045, 2957, 1731, 1606, 1407, 1372, 1250, 1153, 1074, 1043, 972, 928, 859, 836, 756, 734 cm^{-1}; ^1H NMR: (500 MHz, $CDCl_3$) δ 8.25 (br s, 1H, ArN-H), 7.62 (d, 1H, J = 7.1 Hz, ArH), 7.41 (d, 1H, J = 8.1 Hz, ArH), 7.15 (app t, 1H, J = 7.6 Hz, C-6 ArH), 7.06 (br s, 1H, ArH), 4.16 (m, 2H, CO_2CH_2), 3.82 (dd, 1H, J = 5.4 Hz and 8.4 Hz, CHNH), 3.57 (dd, 1H, J = 5.4 Hz and 14.8 Hz, ArCH), 3.22 (dd, 1H, J = 8.4 Hz and 14.8 Hz, ArCH), 1.37 (s, 12H, 4 x Me), 0.94 (m, 2H, CH_2TMS), 0.02 (s, 9H, TMS); ^{13}C NMR: (125 MHz, $CDCl_3$) δ 177.0, 137.7, 131.8, 130.1, 125.8, 122.7, 115.6 114.9, 85.1, 64.5, 57.3, 32.9, 26.46, 26.42, 26.38, 18.9, 0.0; HRMS (ESI-TOF+) exact mass calc. for

[M+H•] ($C_{22}H_{35}N_2O_4BSi$+) requires *m/z* 460.2568, found *m/z* 460.2567; $[\alpha]_D$ = –1.56 (c = 0.95, $CHCl_3$).



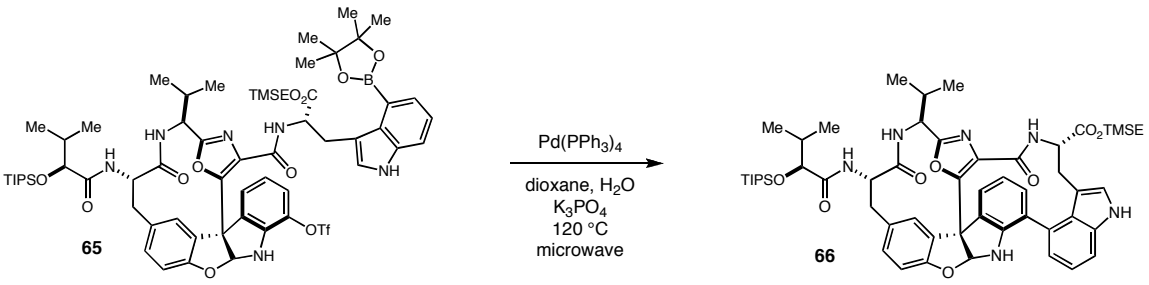
Phenol 64: A 25 mL flask was charged with 202 mg of **10** (0.276 mmol), 124 mg of **63** (0.289 mmol), 44 mg of HOBT•H_2O (0.289 mmol), and 55 mg of EDC•HCl (0.289 mmol). The flask was sealed with a rubber septa and 5.5 mL of DMF was added by syringe under argon. The resulting solution was stirred at room temperature for 15 hours until judged complete by TLC. The reaction mixture was then diluted 100 mL of EtOAc and washed 2 x 50 mL with 0.1 M HCl and 2 x 50 mL with brine. The combined aqueous fractions were then back extracted 2 x 50 mL of EtOAc. The combined organic layer was then washed once with 100 mL of brine and dried over sodium sulfate. Following concentration, the crude solids were purified by flash chromatography on silica gel (40% EtOAc in hexanes) to yield 250 mg (79%) the title compound as an off-white solid. IR (Film): 3401, 2960, 2868, 1736, 1654, 1599, 1503, 1372, 1297, 1250, 1178, 1136, 1062, 859, 838, 755 cm^{-1}; ^1H NMR: (500 MHz, CD_3CN) δ 9.27 (s, 1H, indole N-H), 7.63 (d, 1H, J = 7.8 Hz, N-H), 7.54 (d, 1H, J = 6.5 Hz, Ar-H), 7.50 (d, 1H, J = 8.0 Hz, Ar-H), 7.34 (s, 1H, Ar-H), 7.10 (m, 5H, Ar-H and N-H), 7.00 (m, 1H, N-H), 6.84 (br s, 1H), 6.74 (d, 1H, J = 8.1 H, Ar-H), 6.56 (m, 4H, Ar-H), 5.57 (d, 1H, J = 4.5 Hz, N-H), 4.95 (dd, 1H, J = 6.0 Hz and 9.0 Hz, C**H**NH), 4.64 (dd, 1H, J = 8.0 Hz and 14.5 Hz, C**H**NH), 4.40 (m, 1H, C**H**NH), 4.13 (m, 2H, OC**H₂**CH_2TMS), 4.01 (d, 1H, J = 3.0 Hz, CHOTIPS), 3.55 (m,

2H, 3' indole-C**H**$_2$), 3.13 (dd, 1H, J = 12.0 Hz and 12.0 Hz, tyrosine ArC**H**(CH)NH), 2.74 (dd, 1H, J = 2.5 Hz and 12.0 Hz, tyrosine ArCH(C**H**)NH), 2.19 (m, 1H, C**H**Me$_2$), 1.89 (m, 1H, C**H**Me$_2$), 1.30 (s, 12H, 4 x Me), 1.06 (m, 21H, TIPS), 0.97 (d, 3H, J = 6.6 Hz, CH**Me**(Me)), 0.95 (d, 3H, J = 6.6 Hz, CH**Me**(Me)), 0.90 (m, 2H, **C**H$_2$TMS), 0.84 (d, 3H, J = 6.4 Hz, CH**Me**(Me)), 0.80 (d, 3H, J = 6.7 Hz, CH**Me**(Me)), 0.00 (s, 9H, TMS); ^{13}C NMR: (125 MHz, CD_3CN) δ 171.7, 170.6, 160.1, 159.8, 156.5, 152.5, 140.8, 136.4, 135.9, 130.0, 129.94, 129.92, 129.8, 129.6, 128.4, 128.3, 128.1, 124.8, 121.3, 120.2, 119.9, 114.8, 114.3, 113.7, 111.1, 109.8, 102.6, 83.5, 77.5, 62.7, 55.2, 53.8, 52.3, 38.3, 33.4, 28.0, 26.9, 23.9, 23.7, 18.9, 17.2, 17.1, 16.6, 16.5, 16.4, 11.8, -2.8. HRMS (ESI+) exact mass calc. for [M+H] ($C_{61}H_{85}N_6O_{11}BSi_2$) requires *m/z* 1145.594, found *m/z* 1145.589; $[\alpha]_D^{25} = -36.3$ (c = 2.0, $CHCl_3$).



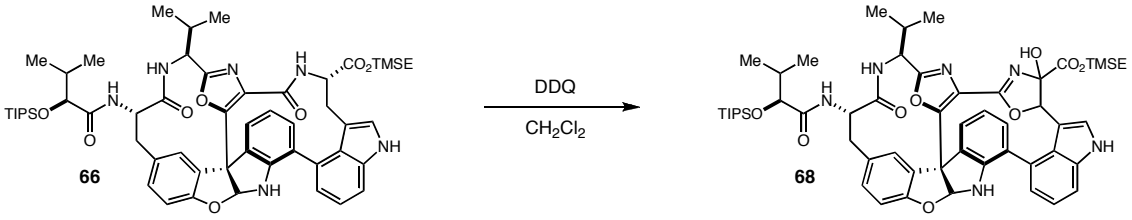
Triflate 65: To a solution of 200 mg of **64** (0.1746 mmol) in 8.75 mL of CH_2Cl_2 was added 120 μL of DIPEA (0.6984 mmol) via syringe. To the resulting solution was added 125 mg of $NPhTf_2$ (0.349 mmol). The resulting solution was stirred at room temperature for 5 hours until judged complete by TLC. The crude reaction was then diluted with 100 mL of EtOAc and 100 mL of saturated $NaHCO_3$. The layers were separated and the aqueous was washed with 2 x 50 mL of EtOAc. The combined organic fractions were

then washed with 100 mL of brine and dried over sodium sulfate. Following concentration the crude solid was purified by flash chromatography on silica gel (25% EtOAc in hexanes) to yield 183 mg (82%) of the title compound as an off-white solid. IR (Film): 3403, 3294, 2961, 2869, 1735, 1655, 1498, 1423, 1372, 1343, 1249, 1211, 1172, 1137, 1062, 914, 882, 859, 838, 755, 684 cm^{-1}; ^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.03 (s, 1H, indole N-H), 7.60 (d, 1H, J = 7.1 Hz, Ar-H), 7.50 (d, 1H, J = 8.6 Hz, Ar-H), 7.45 (d, 1H, J = 1.5 Hz, Ar-H), 7.37 (d, 1H, J = 8.1 Hz, Ar-H), 7.21 (d, 1H, J = 9.4 Hz, Ar-H), 7.12 (dd, 1H, J = 7.5 Hz and 7.5 Hz, Ar-H), 7.09 (s, 1H, OC**H**NH), 7.08 (m, 1H, Ar-H), 7.03 (d, 1H, J = 8.34 Hz, Ar-H), 6.97 (m, 2H, Ar-H and NH), 6.75 (d, 1H, J = 8.1 Hz, Ar-H), 6.67 (t, 1H, J = 7.5 Hz, Ar-H), 6.07 (br s, 1H, NH), 5.49 (d, 1H, J = 4.5 Hz, NH), 4.98 (dd, 1H, J = 5.0 Hz and 9.0 Hz, C**H**NH), 4.81 (m, 1H, C**H**NH), 4.37 (br m, 1H, C**H**NH), 4.10 (m, 3H, OC**H₂**CH_2TMS and CHOTIPS), 3.54 (m, indole 3' Ar-C**H₂**), 3.32 (dd, 1H, J = 12.5 Hz and 12.5 Hz, tyrosine ArC**H**(CH)NH), 2.70 (dd, 1H, J = 3.0 Hz and 12.5 Hz, tyrosine ArC**H**(CH)NH), 2.30 (m, 1H, C**H**Me_2), 1.97 (m, 1H, C**H**Me_2), 1.30 (app d, 12H, J = 3.5 Hz, 4 x Me), 1.05 (m, 24H, TIPS and CH**Me**(Me)), 0.98 (d, 3H, 6.7 Hz, CH**Me**(Me)), 0.96 (d, 3H, 6.7 Hz, CH**Me**(Me)), 0.85 (m, 2H, C**H₂**TMS), 0.82 (d, 3H, CH**Me**(Me)), 0.00 (s, 9H, TMS); ^{13}C NMR: (125 MHz, $CDCl_3$) δ 173.9, 173.6, 173.5, 173.3, 173.2, 161.5, 160.8, 158.7, 153.5, 142.3, 137.4, 134.73, 134..63, 134.58, 134.48, 132.8, 132.0, 131.93, 131.87, 130.7, 129.9, 128.4, 125.6, 123.8, 122.9, 122.6, 121.8, 121.4, 121.1, 118.8, 113.7, 112.3, 104.4, 85.4, 79.5, 65.1, 62.2, 57.5, 54.8, 54.6, 39.9, 38.2, 35.4, 31.3, 30.0, 29.9, 26.4, 26.2, 21.2, 19.6, 19.5, 19.0, 13.9. 0.0; HRMS (ESI+) exact mass calc. for [M+H] ($C_{62}H_{85}N_6O_{13}BF_3SSi_2$) requires *m/z* 1276.5437, found *m/z* 1276.5402; $[\alpha]_D^{25} = -35.9$ (c = 2.0, $CHCl_3$).



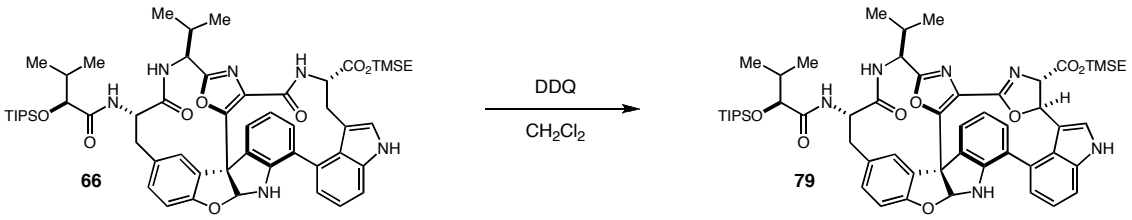
Macrocycle 66: A microwave reactor vessel was charged with 5.0 mg of **65** (.003915 mmol), 1.13 mg of $Pd(PPh_3)_4$ (0.0009788 mmol), and 1.62 mg of K_3PO_4 inside a glove box. The flask was sealed and charged with 0.83 mL of rigorously degassed dioxane and 0.16 mL of rigorously degassed water, both via syringe. The reaction was then heated to 120 °C in a CEM Discover microwave (200W) for 30 minutes. The crude solution was cooled to room temperature and diluted with 25 mL of EtOAc and 50 mL of saturated NH_4Cl solution. The layers were separated and the organic was washed 2 x 25 mL with brine and dried over sodium sulfate. Following concentration, the resulting oil was purified by flash chromatography on silica gel to provide (1:1 EtOAc:hexanes) to yield the title compound as an amorphous tan solid (2.7 mg, 70%). IR (Film): 3402, 3295, 2957, 2868, 1737, 1653, 1512, 1492, 1456, 1348, 1250, 1171, 1097, 1062, 911, 881, 837, 731 cm^{-1}; ^1H NMR: (500 MHz, $CDCl_3$) δ 8.56 (s, 1H, NH), 7.64 (s, 1H, Ar-H), 7.46 (d, 1H, J = 7.2 Hz, Ar-H), 7.40 (d, 1H, J = 8.0 Hz, Ar-H), 7.34 (d, 1H, J = 6.6 Hz, Ar-H), 7.23 (m, 2H, Ar-H), 7.11 (d, 1H, J = 8.3 Hz, Ar-H), 7.05 (d, 1H, J = 6.6 Hz, Ar-H), 7.00 (t, 1H, J = 7.6 Hz, Ar-H), 6.76 (d, 1H, J = 8.2 Hz, Ar-H), 6.20 (br s, 1H, NH), 6.03 (d, 1H, J = 3.0 Hz, OC**H**NH), 5.19 (d, 1H, J = 6.0 Hz, NH), 5.04 (dd, 1H, J = 4.0 Hz and 9.0 Hz, C**H**NH), 4.75 (d, 1H, J = 3.0 Hz, OCHN**H**), 4.46 (m, 1H, C**H**NH), 4.20 (m, 2H, OC**H**$_2$$CH_2$TMS), 4.12 (d, 1H, J = 3.5 Hz, CHOTIPS), 4.08 (m, 1H, C**H**NH), 3.44 (dd,

1H, J = 12.5 Hz and 12.5 Hz, tyrosine ArC**H**(CH)NH), 2.91 (dd, 1H, J = 2.0 Hz and 15.5 Hz, indole 3' ArC**H**(CH)NH), 2.75 (dd, 1H, J = 3.0 Hz and 12.5 Hz, tyrosine ArC**H**(CH)NH), 2.55 (m, 1H, C**H**Me_2), 2.01 (m, 2H C**H**Me_2 and indole 3' ArC**H**(CH)NH), 1.06 (m, 21H, TIPS), 1.00 (d, 3H, J = 6.5 Hz, CH**Me**), 0.96 (d, 1H, J = 7.0 Hz, CH**Me**), 0.89 (d, 1H, J = 7.0 Hz, CH**Me**), 0.81 (d, 1H, J = 7.0 Hz, CH**Me**), 0.00 (s, 9H, TMS); ^{13}C NMR: (125 MHz, $CDCl_3$) δ 173.6, 173.5, 173.4, 163.3, 160.8, 159.1, 152.3, 149.3, 137.5, 134.3, 132.1, 131.9, 131.4, 130.6, 129.6, 128.8, 128.3, 126.6, 125.9, 124.6, 124.5, 123.8, 122.4, 121.8, 114.9, 113.0, 112.0, 105.2, 79.4, 65.3, 62.1, 59.7, 57.7, 55.3, 39.9, 35.2, 29.9, 29.7, 20.9, 19.5, 19.4, 19.0, 18.75, 18.73, 18.6, 13.8, 0.00; HRMS (ESI+) exact mass calc. for [M+H] ($C_{55}H_{73}N_6O_8Si_2$) requires *m/z* 1001.5023, found *m/z* 1001.5008; $[\alpha]_D^{25} = -141.3$ (c = 0.40, $CHCl_3$).



Alcohol 68: To a room temperature solution of **66** (4.5 mg, 0.0045 mmol) in 0.225 mL of CH_2Cl_2 was added DDQ (3.06 mg, 0.0135 mmol) in one portion. The resulting brown solution was stirred at room temperature for 11 hours until judged complete by TLC. The reaction was diluted with 5.0 mL of EtOAc and 2.0 mL of saturated sodium thiosulfate solution. The solution was agitated until the brown color disappears and the remaining solution was bright orange. The layers were separated and the organic layer was washed repeatedly with 5.0 mL portions of saturated $NaHCO_3$ until no more orange coloring was

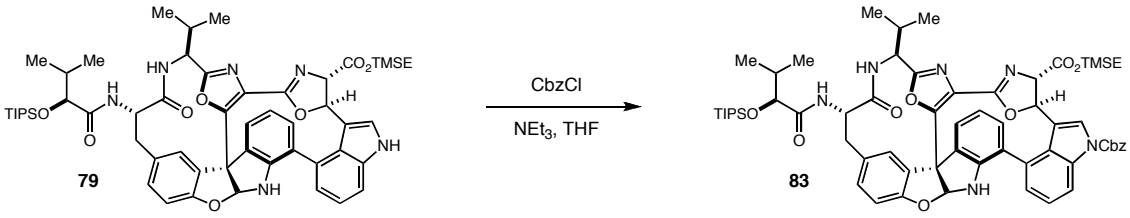
extracted into the aqueous phase. The organic fraction was dried over sodium sulfate, concentrated, and purified by preparative TLC (1:1 ethyl acetate:hexanes) to yield the title compound as a tan solid in 45% yield (2.0 mg). IR (Film): 3402, 2926, 2865, 1729, 1657, 1519, 1489, 1294, 1251, 1148, 1101, 1063, 912, 840, 68, 680 cm^{-1}; ^{1}H NMR: (500 MHz, CD_3CN) δ 9.45 (s, 1H, NH), 8.10 (d, 1H, J = 1.5 Hz, indole C(2)), 7.80 (d, 1H, J = 7.5 Hz, Ar-H), 7.50 (d, 1H, J = 7.5 Hz, Ar-H), 7.46 (d, 1H, J = 8.0 Hz, Ar-H), 7.42 (d, 1H, J = 7.0 Hz, Ar-H), 7.29 (m, 2H, Ar-H), 7.13 (br s, 1H, Ar-H), 7.10 (d, 1H, J = 9.0 Hz, N-H), 6.99 (dd, 1H, J = 1.5 Hz and 8.0 Hz, Ar-H), 6.74 (d, 1H, J = 10.0 Hz, N-H), 6.63 (d, 1H, J = 8.0 Hz, Ar-H, 6.38 (s, 1H, OC**H**NH), 5.30 (dd, 1H, J = 6.0 Hz and 10.0 Hz, C**H**NH), 5.00 (d, 1H, J = 1.5 Hz, ArC**H**O), 4.4 (m, 2H, OCH_2CH_2TMS), 4.13 (m, 1H, C**H**NH), 4.03 (d, 1H, J = 3.5 Hz, CHOTIPS), 3.40 (app t, 1H, J = 12.5 Hz, ArC**H**(H)CHNH), 2.61 (dd, 1H, J = 2.5 Hz and 12.5 Hz, ArC**H**(H)CHNH), 2.24 (m, 1H, C**H**Me_2), 1.94 (m, 1H, C**H**Me_2), 1.05 (d, 3H, J = 7.0 Hz, CH**Me**), 1.03 (m, 21H, TIPS), 0.90 (m, 9H, 3 x CH**Me**), 0.81 (t, 2H, J = 7.5 Hz, CH_2TIPS), 0.00 (s, 9H, TMS); ^{13}C NMR: (125 MHz, CD_3OD) δ 173.74, 173.66, 172.7, 164.3, 163.4, 158.63, 158. 59, 153.7, 151.9, 138.2, 134.0, 131.6, 131.0, 130.9, 130.74, 130.70, 130.6, 130.1, 129.0, 126.2, 125.4, 124.5, 120.24, 120.20, 114.2, 112.7, 112.1, 108.8, 79.6, 68.8, 67.6, 59.0, 57.5, 54.5, 39.5, 35.4, 33.5, 29.3, 21.5, 19.7, 19.6, 19.24, 19.16, 18.9, 0.0; HRMS (ESI+) exact mass calc. for [M+H] ($C_{55}H_{71}N_6O_9Si_2$) requires *m/z* 1014.4743, found *m/z* 1014. 4776; $[\alpha]_D^{25} = -75.7$ (c = 0.147, $CHCl_3$).



66 79

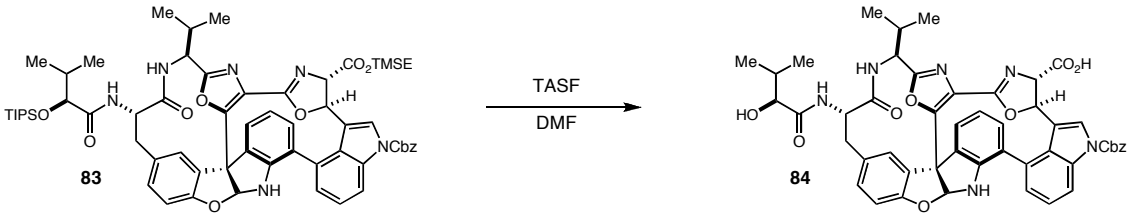
Oxazoline 79: To a solution of **66** (7.0 mg, 0.007 mmol) in 0.7 mL of CH_2Cl_2 was added DDQ (8.4 mg, 0.037 mmol) in one portion. The resulting brown solution was stirred at room temperature for 40 minutes until the reaction was judged complete by TLC. The reaction was diluted with 10 mL of EtOAc and 10 mL of saturated sodium thiosulfate solution. The layers were separated and the organic was washed 5 x 10 mL with saturated $NaHCO_3$ solution until no orange color was extracted into the aqueous phase. The organic layer was washed with 20 mL of brine and dried over sodium sulfate. Following concentration, the resulting brown solids were purified by silica gel chromatography (30% to 100% EtOAc in hexanes) to yield the title compound as an off-white solid (3.9 mg, 56%). IR (Film): 3404, 3302, 2955, 2870, 1732, 1676, 1656, 1563, 1490, 1466, 1385, 1238, 1177, 1096, 1062, 839, 765, 747, 682 cm^{-1}; ^1H NMR: (500 MHz, $CDCl_3$) * In solution, this compound appears to be a hydrolyzed form of the oxazoline, with a benzylic alcohol and a secondary amide. This NMR data reflects this isomeric form. δ 8.04 (br s, 1H, Ar-H), 7.55 (d, 1H, J = 7.0 Hz, Ar-H), 7.45 (d, 1H, J = 8.0 Hz, Ar-H), 7.28 (m, 2H, Ar-H), 7.17 (M, 2H, Ar-H), 6.86 (dd, 1H, J = 2.0 Hz and 8.0 Hz), 6.46 (d, 1H, J = 8.5 Hz, Ar-H), 6.20 (s, 1H, OCHNH), 5.85 (d, J = 10 Hz, NH), 5.75 (d, 1H, J = 8.5 Hz, TMSEOC(O)C**H**NH), 5.30 (app t, J = 10.0 Hz, C**H**NH), 5.14 (dd, 1H, J = 8.5 Hz and 12.0 Hz, TMSEOC(O)C**H**NH), 4.88 (d, 1H, J = 12 Hz, Ar-C(**H)**OH), 4.22 (m, 2H, OC**H₂**CH_2TMS), 4.17 (d, 1H, J = 3.5 Hz, CHOTIPS), 4.10 (m, 1H, C**H**NH), 3.46 (dd, 1H, J = 12.5 Hz and 12.5 Hz, ArC(**H**)HNH), 2.55 (dd, 1H, J = 3.0 Hz and 12.5 Hz,

ArC(**H**)HNH), 2.33 (m, 1H, C**H**Me_2), 2.05 (m, 1H, C**H**Me_2), 1.10 (m, 24H, TIPS and C$\mathbf{H_2}$TMS), 0.98 (m, 12H, 4 x CH**Me**), 0.00 (s, 9H, TMS); ^{13}C NMR: (125 MHz, CD_3CN) δ 171.6, 170.6, 168. 9, 164.8, 163.0, 155.8, 155.6, 153.8, 136.7, 134.8, 130.8, 129.4, 129.2, 129.1, 128.8, 127.4, 127.0, 126.4, 125.4, 122.8, 121.9, 118.7, 166.7, 115.1, 110.8, 108.9, 105.6, 77.6, 66.0, 64.1, 59.8, 59.6, 55.0, 54.8, 52.4, 38.1, 33.5, 28.0, 19.0, 17.6, 17.2, 17.1, 16.7, 16.5, 16.3, 13.2, 13.1, 11.9, -3.0; HRMS (ESI+) exact mass calc. for [M+H] ($C_{55}H_{71}N_6O_8Si_2$) requires *m/z* 999.4794, found *m/z* 999.4786; $[\alpha]_D^{25} = -150.1$ (c = 0.456, $CHCl_3$).



Oxazoline 83: To a room temperature solution of **79** (3.9 mg, 0.0039 mmol) in 0.4 mL THF was added NEt_3 (3.3 μL, 0.0234 mmol), DMAP (0.48 mg, 0.0039 mmol), and CbzCl (2.2 μL, 0.0234 mmol). The resulting heterogeneous white solution was stirred for five hours at room temperature until judged complete by TLC. It was then diluted with 5.0 mL of EtOAc and 5.0 mL of 0.5 M HCl. The layers were separated and the aqueous layer was washed 2 x 5.0 mL with EtOAc. The combined organics were washed 2 x 10 mL with brine, dried over sodium sulfate, and concentrated. The resulting solids were purified by silica gel chromatography (20%–35% EtOAc in hexanes) to give the title compound as an off-white solid in 73% yield (3.2 mg). IR (Film): 3406, 3333, 2960, 2868, 1733, 1696, 1658, 1491, 1422, 1389, 1357, 1289, 1241, 1179, 11126, 1068, 963,

914, 881, 839, 772, 694 cm^{-1}; ^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.162 (br s, 1H, Ar-H), 8.05 (d, 1H, J = 1.5 Hz, Ar-H), 7.9 (d, 1H, J = 8.0 Hz, Ar-H), 7.63 (br s, 1H, Ar-H), 7.57 (app t, 1H, J = 6.5 Hz, Ar-H), 7.50–7.25 (m, 5H, Ar-H), 7.22 (d, 1H, J = 9.0 Hz, Ar-H), 6.88 (dd, 1H, J = 2.0 Hz and 7.0 Hz, Ar-H), 6.48 (d, 1H, J = 8.0 Hz, Ar-H), 6.17 (s, 1H, OC**H**NH), 5.89 (d, 1H, J = 10 Hz, NH), 5.81 (d, 1H, J = 8.5 Hz, NH), 5.55 (d, 1H, J = 12 Hz, CH(H)OBn), 5.40 (d, 1H, J = 12 Hz, CH(H)OBn), 5.31 (app t, 1H, J = 10.0 Hz, C**H**NH), 5.15 (dd, 1H, J = 10.0 Hz and 6.5 Hz, C**H**NH), 4.68 (d, 1H, J = 11.5 Hz, ArCHOH), 4.22 (m, 2H, OC**H**$_2$$CH_2$TMS), 4.18 (d, 1H, J = 3.5 Hz, CHOTIPS), 4.11 (m, 1H, CH_2C**H**NH), 3.47 (dd, 1H, J = 13.0 Hz and 13.0 Hz, CH(**H**)CHNH), 2.56 (dd, 1H, J = 3.0 Hz and 13.0 Hz, CH(**H**)CHNH), 2.36 (m, 1H, C**H**Me_2), 2.07 (m, 1H, C**H**Me_2), 1.12 (d, 3H, J = 6.5 Hz, CH**Me**), 1.10–1.00 (m, 32H, TIPS, 3 x C**H**Me_2, C**H$_2$**TMS), 0.00 (s, 9H, TMS); ^{13}C NMR: (125 MHz, $CDCl_3$) δ 173.6, 173.4, 170.5, 167.0, 164.6, 157.88, 157.85, 155.6, 137.0, 136.5, 131.5, 131.4, 131.2, 130.53, 130.48, 130.45, 130.35, 130.33, 130.2, 130.0, 129.8, 129.6, 129.5, 128.7, 127.7, 127.6, 124.6, 124.5, 122.1, 116.6, 111.7, 107.1, 79.7, 70.5, 68.7, 67.0, 57.1, 56.5, 55.0, 39.6, 35.4, 29.5, 21.8, 20.3, 19.7, 19.6, 19.2, 19.0, 18.7, 14.0, 0.0; HRMS (ESI+) exact mass calc. for [M+H] ($C_{63}H_{76}N_6O_{10}Si_2$) requires *m/z* 1132.516, found *m/z* 1132.517; $[\alpha]_D^{25}$ = –171.5 (c = 0.45, $CHCl_3$). Note: The H-NMR spectral data indicate that the oxazoline in product was a ring-opened hydroxy amide form in $CDCl_3$. This contradicts the HRMS data and the behavior of the compounds by TLC. It was assumed that these species were in equilibria due to acidic impurities in the chloroform.



Carboxylic Acid 84: To a solution of the **83** (3.2 mg, 0.00282 mmol) in 0.2 mL of DMF was added 0.15 mL of a TASF solution (1.72 mg, 0.00622 mmol) in DMF via syringe under argon. After stirring for 35 minutes at room temperature the reaction was judged complete by TLC and diluted with 2.0 mL EtOAc, 0.5 mL of AcOH, and 1.0 mL of H_2O. The layers were separated and the aqueous layer was washed 2 x 5 mL with EtOAc, and the combined organic was washed twice with 10 mL of brine. The resulting solution was dried over sodium sulfate and concentrated *in vacuo*. The resulting crude solids were purified by chromatography on silica gel (99:1 MeCN:AcOH) to yield the title compound as a translucent yellow solid in 77% yield (1.9 mg). IR (Film): 3274 (br), 1656, 1423, 1292, 1246, 1127, 746 cm^{-1}; ^1H NMR: (500 MHz, CD_3OD) δ 8.05 (br s, 1H, Ar-H), 7.96 (d, 1H, J = 1.5 Hz, indole C(2) Ar-H), 7.86 (app d, 1H, J = 8.5 Hz, Ar-H), 7.79 (s, 1H, Ar-H), 7.55 (dd, 1H, J = 2.5 Hz and 7.5 Hz, Ar-H), 7.50 (d, 1H, J = 7.5 Hz, Ar-H), 7.44–7.42 (m, 2H, Ar-H), 7.35–7.23 (m, 3H, Ar-H), 7.19 (m, 1H, Ar-H), 6.84 (d, 1H, J = 8.0 Hz, Ar-H), 6.39 (d, 1H, J = 8.0 Hz, Ar-H), 5.96 (s, 1H, OC**H**NH), 5.37 (br s, 2H, OCH_2Ph), 5.12 (d, 1H, J = 10 Hz, C**H**NH), 4.84 (d, 1H, J = 11.5 Hz, NC**H**CO_2H), 4.71 (d, 1H, J = 11.5 Hz, ArC(**H**)OCHCO_2H), 4.12 (dd, 1H, J = 3.0 Hz and 11.5 Hz, C**H**NH), 3.76 (d, 1H, J = 4.0 Hz, C**H**OH), 3.31 (app t, 1H, J = 11.5 Hz, ArC(**H**)HCHN), 2.52 (dd, 1H, J = 3.0 Hz and 11.5 Hz, ArC(**H**)HCHN), 2.20 (m, 1H, C**H**Me_2), 1.97 (m, 1H, C**H**Me_2), 1.11 (d, 3H, J = 6.5 Hz, C**H**Me), 0.93 (d, 3H, J = 6.5 Hz, C**H**Me), 0.90 (d, 3H, J = 7.0 Hz, C**H**Me), 0.78 (d, 3H, J = 7.0 Hz, C**H**Me); ^{13}C NMR: (125 MHz, CD_3OD) δ

175.6, 174.5, 166.7, 165.4, 157.9, 157.6, 155.3, 152.3, 137.6, 136.9, 136.6, 132.3, 131.7, 131.1, 130.9, 130.4, 130.3, 129.8, 129.7, 129.5, 129.3, 128.5, 128.1, 126.7, 126.6, 123.9, 123.7, 123.3, 76.8, 69.9, 67.6, 61.7, 61.6, 58.1, 56.8, 54.8, 38.9, 33.2, 29.3, 20.6, 19.6, 19.2, 16.4, 14.5. HRMS (ESI+) exact mass calc. for [M+H] ($C_{49}H_{45}N_6O_{10}Si_2$) requires *m/z* 876.3119, found *m/z* 876.3120; $[\alpha]_D^{25} = -116.0$ (c = 0.1545, 10:1 $CHCl_3$:MeOH).

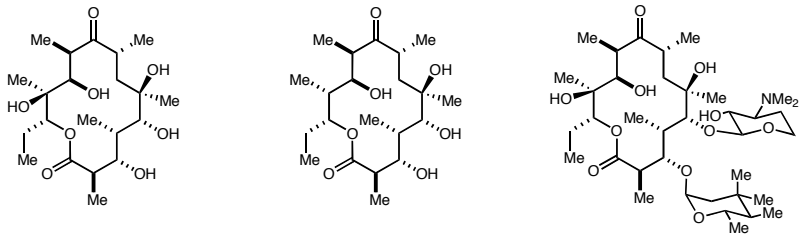
Chapter 6

Synthetic Investigations of Erythronolide B: Investigations of a Diastereoselective, Late-Stage Aldol Reaction

I. Background

The erythrolide antibiotics are metabolites of the fungus *Streptomyces erythreus* that were first isolated in 1952 and structurally elucidated several years later.[1] They have a prominent history in modern medicine as powerful antibacterial agents, finding application in the treatment of human illnesses ranging from acne to pneumonia. In light of these interesting biological properties and uniquely complex molecular architectures, this family of molecules has also become a classic target set for chemical synthesis.

Figure 1: The erythronolides



Erythronolide A (**1**) Erythronolide B (**2**) Erythromycin A (**3**)

In particular, the stereochemical relationships along the erythronolide backbone have served as both an inspiration and testing ground for chemical methodologies

[1] (a) McGuire, J. M.; Bunch, R. L.; Anderson, R. C.; Boaz, H. E.; Flynn, E. H.; Powell, H. M.; Smith, J. W. *Antiobiotics and Chemotherapy* **1952**, *2*, 218–283. (b) Wiley, P. F.; Gerzon, K.; Flynn, E. H.; Sigal, M. V.; Quarck, U. C. *J. Am. Chem. Soc.* **1955**, *77*, 3677–3678. (c) Wiley, P. F.; Weaver, O. *J. Am. Chem. Soc* **1955**, *77*, 3422–3423. (d) Gerzon, K.; Flynn, E. H.; Sigal, M. V.; Wiley, P. F.; Monahan, R.; Quarck, U. C. *J. Am. Chem. Soc.* **1956**, *78*, 6396–6408. (e) Wiley, P. F.; Weaver, O. *J. Am. Chem. Soc* **1956**, *78*, 808–810. (f) Wiley, P. F.; Gale, R.; Pettinga, C. W.; Gerzon, K. *J. Am. Chem. Soc*. **1957**, *79*, 6074–6077. (g) Wiley, P. F.; Gerzon, K.; Flynn, E. H.; Sigal, M. V.; Weaver, O.; Quarck, U. C.; Chauvette, R. R.; Monahan, R. *J. Am. Chem. Soc* **1957**, *79*, 6062–6070. (h) Wiley, P. F.; Sigal, M. V.; Weaver, O.; Monahan, R.; Gerzon, K. *J. Am. Chem. Soc.* **1957**, *79*, 6070–6074.

focused upon the production and control of stereogenicity. As strategies and methods for the controlled installation of stereochemistry progressed throughout the decades, many were applied to challenges posed by the erythronolides, including the use of cyclic stereocontrol, chiral pool approaches, and iterative aldol/allylation chemistry.[2,3,4] Yet these approaches generally require that each stereocenter, or set of stereocenters, be installed individually in a distinct reaction, or step. Though this strategic approach is effective and easily adaptable to the extant theoretical models of asymmetric induction, it is often far from efficient. It often requires extensive protecting group manipulations and oxidation state adjustments that can often make up a substantial fraction of the overall number of synthetic operations.

A promising and distinct approach is one wherein the multiple stereochemical elements can be installed directly in a single step through the use of tandem reaction sequences. Ideally, in such a process the product of an initial transformation is utilized as the starting material for a subsequent one, and so on, with no isolation steps in between. This can often bypass the problems of differential reactivity that lead to aforementioned inefficiencies, and allow for the installation of more complexity with less expenditure of time, effort, and resources. Thus, the MacMillan group realized that the classical erythronolide family of targets was an ideal platform from which to highlight the utility of their recently developed and highly stereoselective tandem acyl-Claisen rearrangement. This methodology could provide diastereoselective access to the entire

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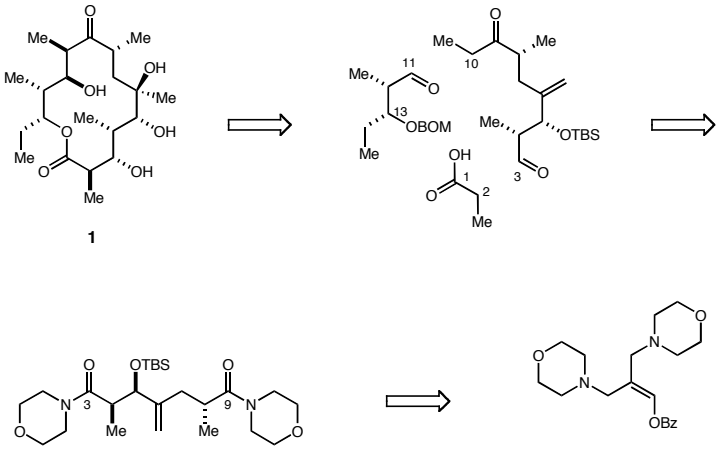
[2] Martin, S. F.; Pacofsky, G. J.; Gist, R. P.; Lee, W. C. *J. Am. Chem. Soc*. **1989**, *111*, 7634–7636.

[3] Kochetkov, N. K.; Sviridov, A. F.; Ermolenko, M. S.; Yashunsky, D. V.; Borodkin, V. S. *Tetrahedron* **1989**, *45*, 5109–5136.

[4] Mulzer, J.; Kirstein, H. M.; Buschmann, J.; Lehmann, C.; Luger, P. *J. Am. Chem. Soc.* **1991**, *113*, 910–923.

C(3)-C(9) portion of the erythronolide backbone in a single, elegant synthetic operation (*vide infra).*

Figure 2: Tandem acyl Claisen route to erythronolide B



Yet before discussing the specifics of our synthetic strategy in detail, it would be illustrative to discuss two of the completed, prior syntheses of these molecules. Besides being landmark accomplishments in the field of total synthesis, these works also provide the context for our own work. Specifically, discussion of the Corey group synthesis of erythronolide B in 1978 and the Woodward group synthesis of erythromycin A in 1981 will furnish a pertinent background into the chemistry of these molecules and act to provide some perspective into the advantages engendered in our own approach.

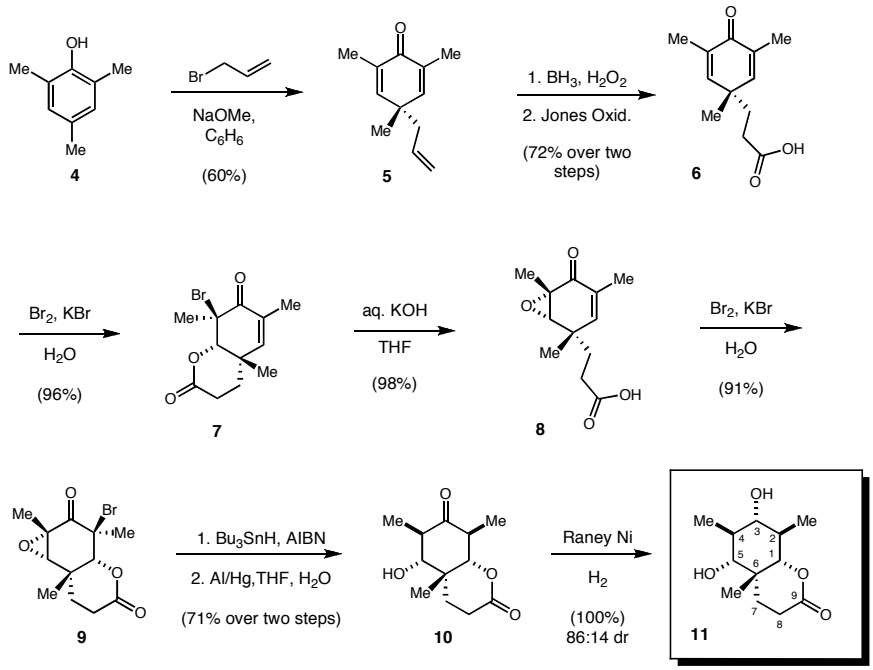
II. Corey's Synthesis of Erythronolide B

The synthesis of erythronolide B in the late 1970s by E. J. Corey and his coworkers at Harvard is a truly remarkable and historically important chapter in the field of complex molecule synthesis.[5] This work was not only groundbreaking given the

[5] Corey, E. J.; Kim, S.; Yoo, S. E.; Nicolaou, K. C.; Melvin, L. S.; Brunelle, D. J.; Falck, J. R.; Trybulski, E. J.; Lett, R.; Sheldrake, P. W. *J. Am. Chem. Soc* **1978**, *100*, 4620–4622.

complexity of the target, but for the profound and deliberate way that it addressed the most challenging elements of the molecule by the development of new reagents and methods to enable its completion. The Corey synthesis commenced with a *para*-selective allylation of 2,4,6-trimethylphenol **4** with allyl bromide in benzene to furnish dienone **5** (Scheme 1). Hydroboration of the newly installed olefin followed by oxidation of the resulting alcohol furnished carboxylic acid **6**. Subsequent treatment with aqueous bromine led to a diastereoselective bromolactonization that gave racemic **7** in high chemical yield. Exposure of this product to aqueous base opened the lactone ring and the transient alkoxide that was formed displaced the vicinal bromide to form epoxy acid **8**. Ketone **8** can undergo a second diastereoselective bromolactionization in an iterative manner to form **9**.

Scheme 1: Early steps of Corey's synthesis

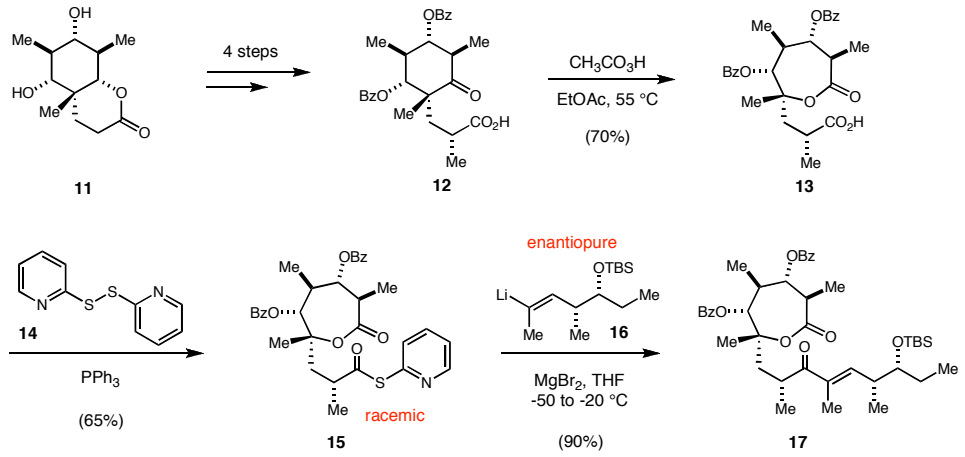


Radical dehalogenation of **9** was followed by reductive epoxide opening using Al/Hg amalgam in aqueous THF to give **10**. Treatment of this adduct with Raney Nickel

under a hydrogen atmosphere efficiently and selectively reduced the remaining ketone to an 86:14 mixture of diastereomers favoring the correct configuration for the erythronolides, **11**. Thus, in short order Corey was able to take a simple aromatic compound and generate a fully substituted cyclohexane in which all six carbons map directly on to the stereochemical framework of erythronolide B.

After several straightforward synthetic operations **11** was transformed into ketoacid **12** (Scheme 2). Treatment of this unsymmetrical ketone with peroxyacetic acid in hot ethyl acetate led to a regiospecific Baeyer-Villiger oxidation furnishing seven-membered lactone **13** in good yield. This elegant transformation breaks open the functionalized cyclohexane to produce a self-protected nine-carbon chain that constitutes the entire right side of the molecule, while concurrently installing the hydroxyl center at C(6) in a stereospecific manner.

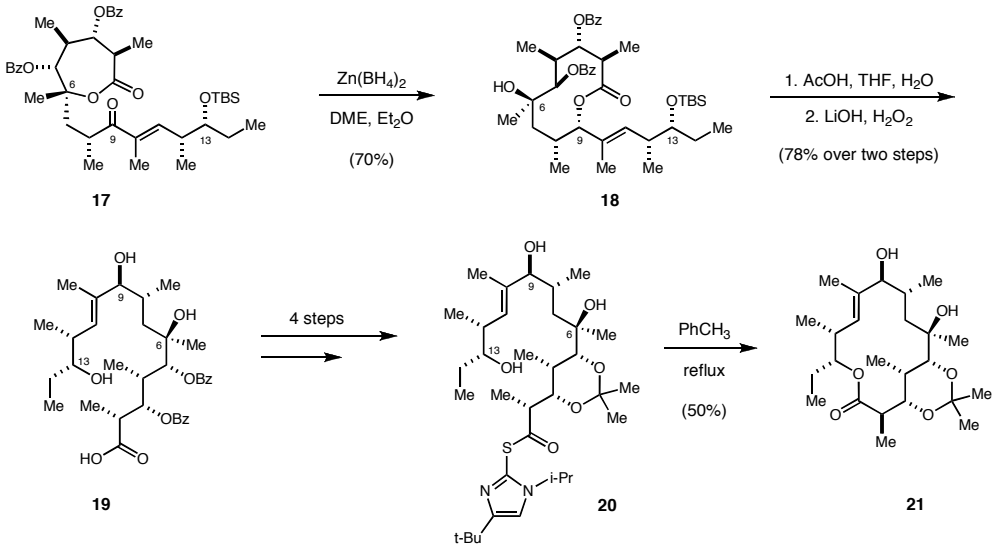
Scheme 2: Resolution of racemic intermediate



The free acid of this oxidation product was then transformed into its 2-pyridine thiol ester **15**. Treatment of this racemic thioester with enantiomerically pure vinyl lithium **16** gave ketone **17** with no observable over-addition products. The diastereomers

arising from this step could be separated chromatographically, yielding enantioenriched material to carry through the rest of the synthesis. Selective reduction of the ketone at C(9) under the action of zinc borohydride created an alkoxide which underwent transesterification with the lactone carbonyl, expanding the seven-membered ring into the ten-membered lactone **18** (Scheme 3). Removal of the silyl ether and saponification of this newly formed lactone yielded free carboxylic acid **19**, primed for macrolactonization. The free acid was transformed into its imidazoyl thioester **20**, which, when heated in dry toluene, furnished macrolactone **21** which was only a few short transformations from the complete natural product.

Scheme 3: Ring expansion and macrolactonization

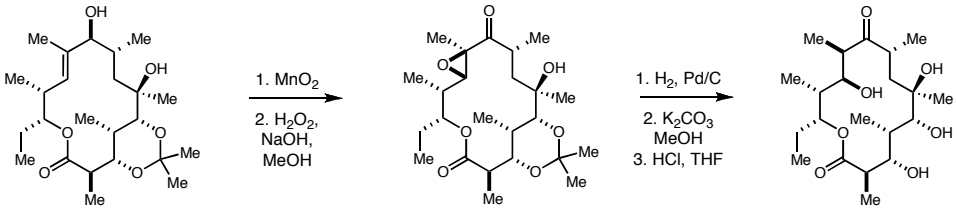


The key to this macrolactonization strategy is the activation of both reactive functionalities by the heterocyclic thioester in **20**. The basic nitrogen of the imidazole ring facilitates deprotonation of the alcohol nucleophile, and upon protonation activates the carbonyl electrophile by means of an intramolecular hydrogen bond. This double

activation strategy was key to the successful completion of the molecule and offered a general solution to a long-standing problem in the field of large ring synthesis.

With all the carbons of the natural product in place, the Corey group pushed onward. Oxidation of the free alcohol at C(9) was followed by nucleophilic epoxidation under the action of peroxide and base (Scheme 4). Reductive opening of the resulting epoxide **23** furnished the C(11) alcohol with the correct requisite stereochemistry, however the C(10) methyl group was produced as a mixture of epimers. Treatment with mild aqueous base epimerized this center to the thermodynamic conformation found in the natural product. A final deprotection of the remaining acetonide gave the natural product in a total of 31 steps and overall yield of less than 0.5%.

Scheme 4: Corey's erythronolide B endgame



22 **23** erythronolide B

III. Woodward's Synthesis of Erythromycin A

Woodward's synthesis of the more complicated glycosylated natural product, erythromycin A was also a landmark event in synthetic organic chemistry.[6,7,8] Completed after his death, Woodward's work took strategic advantage of symmetry elements present in the target, allowing asymmetric construction of the C(3)-C(7) as well as the C(8)-

[6] Woodward, R. B., et al. *J. Am. Chem. Soc* **1981**, *103*, 3210–3213.

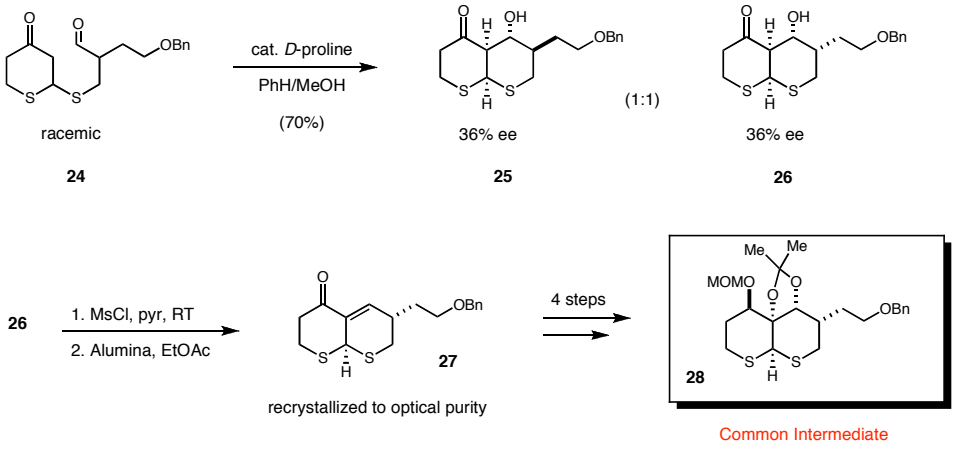
[7] Woodward, R. B., et al. *J. Am. Chem. Soc* **1981**, *103*, 3213–3215.

[8] Woodward, R. B., et al. *J. Am. Chem. Soc* **1981**, *103*, 3215–3217.

C(13) stereocenters from a common precursor. A brief summary of the Woodward route to the seco acid of erythronolide A will serve to outline this synthetic strategy and simultaneously highlight the burgeoning understanding of diastereoselective aldol reactions that occurred in the late 1970s, as this presently remains the dominant strategy toward this class of molecules.

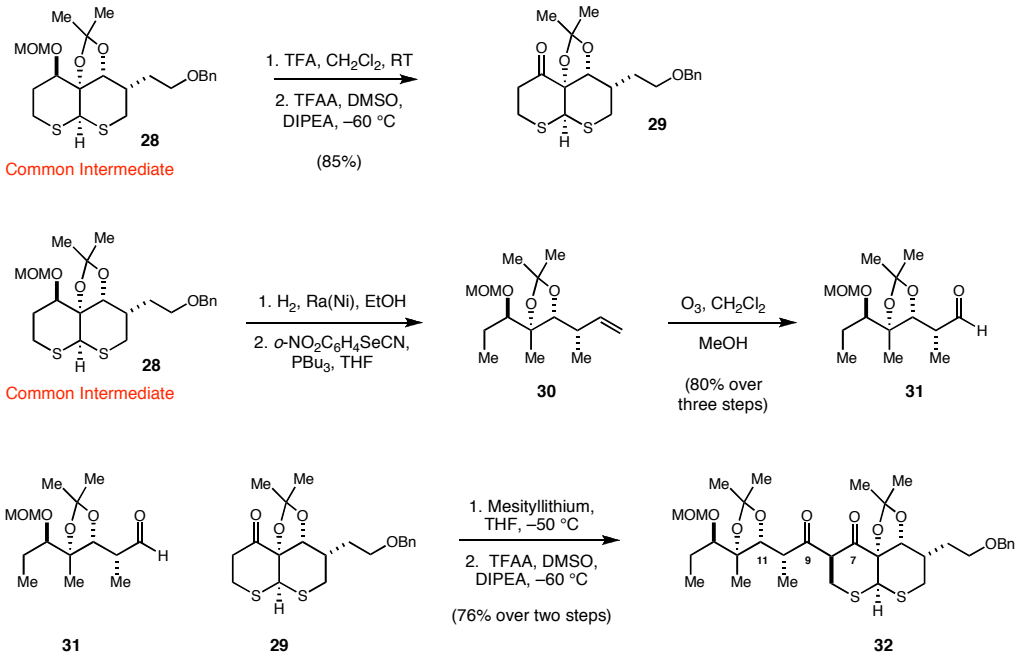
Exposure of racemic ketoaldehyde **24** to *D*-proline in a mixture of benzene and methanol yielded two optically active aldol products, **25** and **26** as a 1:1 mixture in 36% ee (Scheme 5). This remarkable result is believed to arise from a dynamic kinetic resolution of the thioether stereocenter via enamine β-elimination, followed by conjugate additon into the resulting chiral iminium ion and an intramolecular aldol reaction.

Scheme 5: Woodward's synthesis of key intermediate



Following separation of the diastereomers, the one having the desired configuration (**26)** was dehydrated and then recrystallized to afford the optically pure ketone **27**. From this stage only a handful of synthetic operations were needed to access common building block **28** that was the centerpiece of the Woodward strategy.

Scheme 6: Woodward's differentiation of common intermediate

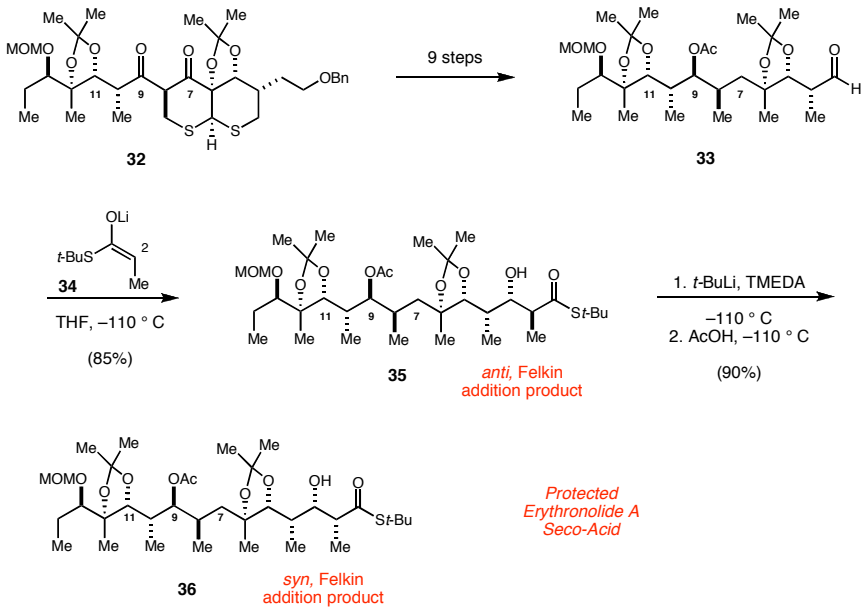


From this common precursor Woodward and his coworkers were able to construct the stereochemical arrays found in the C(4)-C(6) section and the C(10)-C(13) fragment of the seco acid. Precursor **28** was readily transformed into **29** and **31**, which were then in turn joined by a stereoselective aldol condensation. Oxidation of the aldol product gave diketone **32** as a single diastereomer in good yield.

Over the course of nine steps the C(7) ketone of **32** was reduced to its corresponding methylene, the sulfur bicycles were cleaved under the action of Raney nickel leaving behind the correctly configured methyl groups, and the C(2) oxygen was elaborated to aldehyde **33**. Subjection of this aldehyde to the (*E*)-lithium enolate **34** gave the expected *anti*-aldol, Felkin adduct **35** (Scheme 7). Subsequent enolization of the resulting product followed by kinetic protonation epimerized the C(2) stereocenter to the correct configuration of the natural product, thus completing the entire carbon framework and stereochemical array of the natural product aglycone, erythronolide A.

Woodward went on to carry out extensive studies on the macrocyclization step and appendage of the sugar moieties, but this work is beyond the scope of this report. Taken together the Woodward and Corey syntheses demonstrate two distinctly creative and classical approaches towards these molecules. However, there are several aspects of these syntheses that are less impressive by modern standards. Firstly both groups relied heavily on cyclic stereocontrol to enforce the proper diastereoselection. While this is a viable and successful method it often leads to lengthy synthetic sequences. As such it has largely been supplanted in recent years by successful models for predicting high levels of acyclic stereocontrol. Furthermore asymmetric technologies have negated the necessity for classical resolution in synthesis, allowing for greater atom economy.

Scheme 7: Woodward's completion of the seco acid



These factors were born in mind at the outset of the MacMillan synthesis towards erythronolide B. First and foremost this effort was aimed at illustrating the viability of the tandem acyl-Claisen rearrangement as a powerful method for construction of complex

acyclic architectures with high levels of stereocontrol.[9] This would represent the first use of Claisen rearrangement as a key strategy towards the synthesis of an erythrolide antibiotic. Were this strategy successful, asymmetric variants of the tandem Claisen would be investigated, hopefully leading to a concise asymmetric synthesis of erythronolide B.

IV. Preface to MacMillan Retrosynthesis

The MacMillan synthesis, as it is reported here, was devised, executed, and completed by graduate student Vy M. Dong from 2000–2003.[10] The work summarized in the forthcoming section came in attempting to replace a late stage auxiliary-based aldol condensation in her synthetic route with a substrate-controlled, diastereoselective variant. However, to obtain the advanced material needed to investigate this late-stage step, it was necessary to repeat her synthetic route up until the point of investigation. Herein, the overarching synthetic strategy and forward synthesis will be described along with a detailed discussion of the late-stage aldol reaction to install the C(1)-C(2) segment of the seco acid. It should be also be noted that there are three other more recent, completed syntheses of erythronolide B by Kotchekov, Mulzer, and Martin, but discussion of these syntheses are beyond the scope of this report.[2,3,4]

V. MacMillan Retrosynthetic Analysis of Erythronolide B

The MacMillan retrosynthesis begins with the opening of the fourteen-membered macrolactone across its ester linkage (Figure 3). This produces the seco-acid of the

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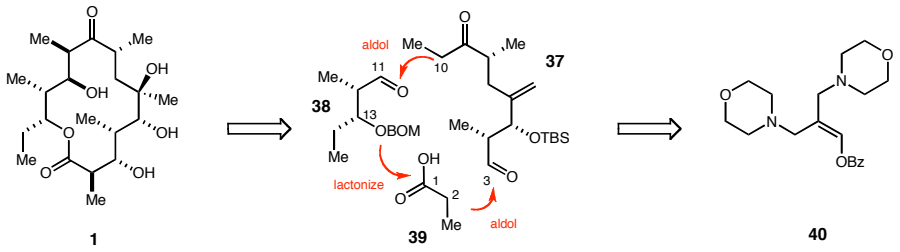
[9] Dong, V. M.; MacMillan, D. W. C. *J. Am. Chem. Soc* **2001**, *123*, 2448–2449.

[10] Dong, V. M. *Ph.D. Thesis*, California Institute of Technology, 2003.

natural product that was envisioned to arise from three major bond constructions employing propionate **39**, known propionaldehyde dimer **38**, and ketone **37**. The union of ketone **37** with fragments **38** and **39** will rely on a series of stereoselective aldol reactions. Ketone **37** was envisioned to arise from a tandem acyl-Claisen rearrangement developed in the MacMillan lab, retrosynthetically yielding bisallylic amine **40**.

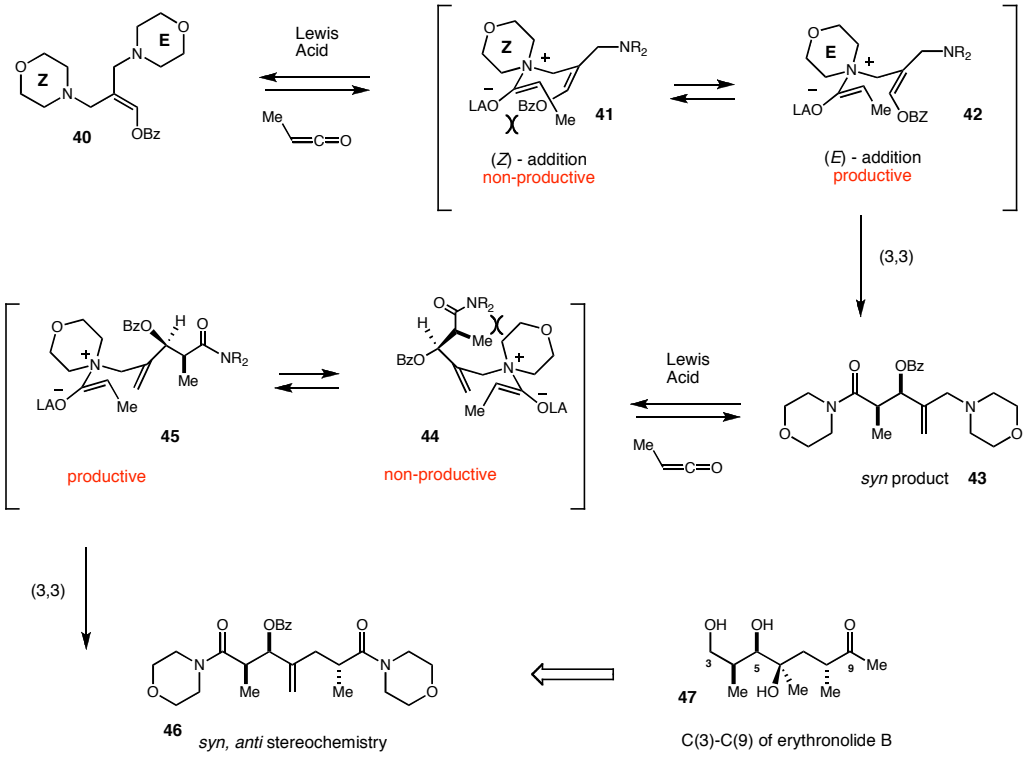
Figure 3: MacMillan Retrosynthesis of erythronolide B



The tandem acyl-Claisen rearrangement used in the construction of the C(3)-C(9) fragment is truly the cornerstone of this synthetic strategy (Scheme 8). This variant of the Claisen rearrangement involves the use of bisallylic amines that add reversibly to electrophilic ketenes in a stereospecific fashion to furnish zwitterionic intermediates that rapidly undergo sigmatropic bond reorganization at ambient temperatures (Scheme 8). Although the first ketene addition is rapid and reversible, only addition at the amine (*E*) to the olefinic substituent (**41**) rearranges due to the avoidance of diaxial interactions in the transition state. A second equivalent of ketene can then react with the remaining allylic amine yielding two possible transition state pathways. Minimization of A(1,2) strain in each chair transition state yields the transition state structures **44** and **45** as shown in Scheme 8. While **44** has its side chain pointing directly into the center of the transition state, **45** undergoes no such unfavorable interactions and productive bond reorganization occurs selectively through this manifold to give the bisamide **46** with

excellent diastereoselectivity. From the product structure it is easy to see how this fragment could be readily elaborated to construct this portion of erythronolide B backbone **47**.

Scheme 8: Tandem acyl Claisen route to C(3)-C(9)

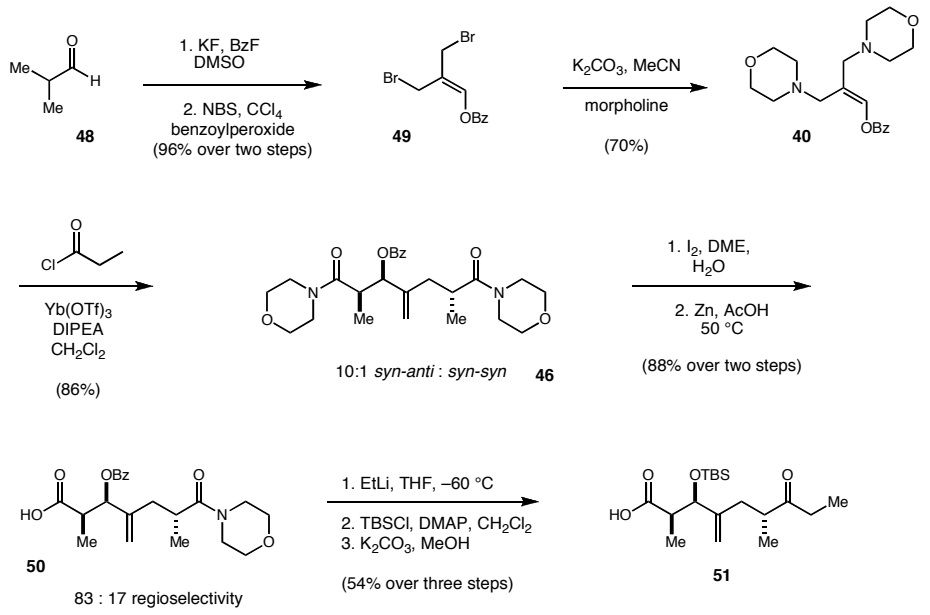


VI. Synthesis

The synthesis commences with the benzoylation of the enol ether derived from isovaleraldehyde (Scheme 9). The product undergoes radical bromination at each of the two allylic methyl positions and these bromides are subsequently displaced by morpholine to yield bisamine **40** in an overall yield of 68% over the three steps. Treatment of **40** with propionyl chloride, Hünig's base, and two equivalents of $Yb(OTf)_3$ yielded 86% of the racemic tandem Claisen product **46** as a 10:1 mixture of

diastereomers, the major possessing the desired *2,3-syn* and *3,6-anti* relative stereochemical relationship.

Scheme 9: Outset of MacMillan synthesis

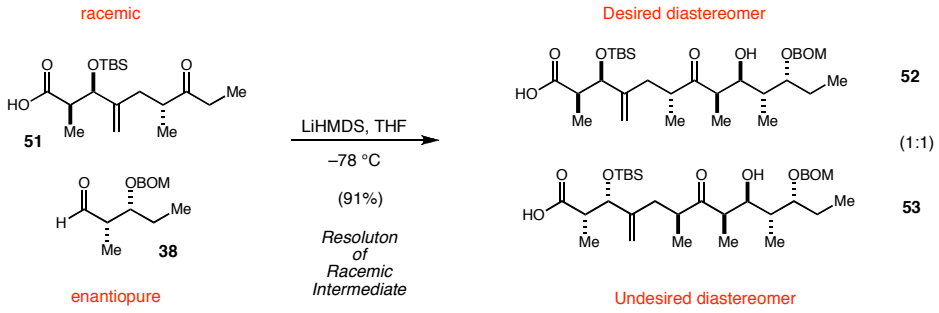


Treatment of the Claisen adduct **46** with iodine in a mixture of DME and water affects an iodolactonization that differentiates the two morpholine amides with moderate regioselectivity (83:17). Reductive opening of the iodolactone with zinc in acetic furnishes carboxylic acid **50** in 88% yield over two steps. Following separation of the regioisomers, the desired amide **50** was treated with freshly prepared ethyl lithium to form ethyl ketone with concomitant removal of benzoate protecting group. The morpholine amide acts to stabilize the initial carbanion addition product by keeping it tetrahedral until aqueous workup, eliminating problems of over-addition. Reprotection of the secondary alcohol followed by basic hydrolysis of the silyl ester gives carboxylic acid **51** in a yield of 54% over three steps.

In order to resolve the enantiomers of ethyl ketone **51**, they were subjected to an aldol reaction with enantiopure aldehyde **38** (Scheme 10). Treatment of **51** with two

equivalents of LiHMDS in cold THF selectively generated the (*Z*)-enolate that condensed with **38** to give the desired *syn*, anti-Felkin aldol adduct **52** along with an equal amount of undesired diastereomer **53**. This stereochemical outcome was analogous to that found by the Martin group in a similar aldol condensation encountered in their studies on the erythronolides.[15]

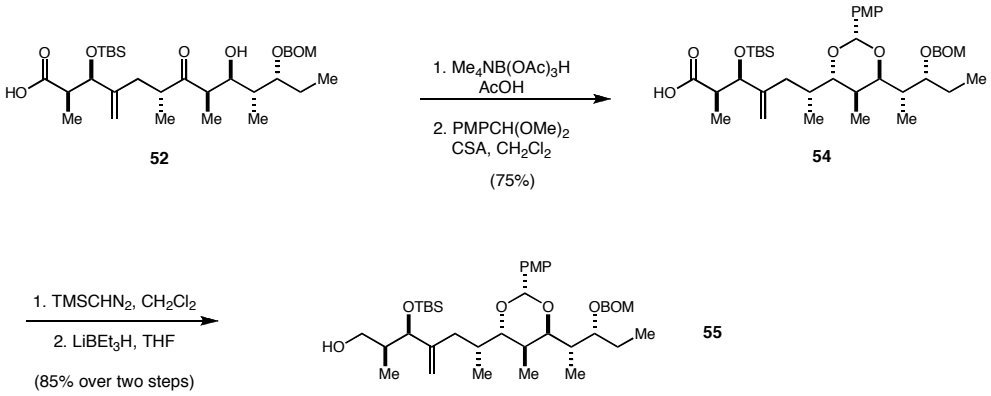
Scheme 10: Resolution of racemic intermediate 51



The aldol products were not separable at this stage and were carried on as a mixture. Selective reduction to the *anti*-diol under the action of tetramethylammonnium-triacetoxtyborohydride, according to the procedure of Evans, followed by protection of the newly formed diol as its *p*-methoxyphenyl acetal **54**, furnished separable diastereomers in good chemical yield over two steps (Scheme 11).[11] Esterification of enantiopure carboxylic acid with $TMSCHN_2$, followed by reduction of the newly formed methyl ester, gave primary alcohol **55** in 85% yield over the two steps. Oxidation of this alcohol furnishes the electrophilic aldehyde required to explore the aforementioned aldol reaction.

[11] Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc* **1988**, *110*, 3560–3578.

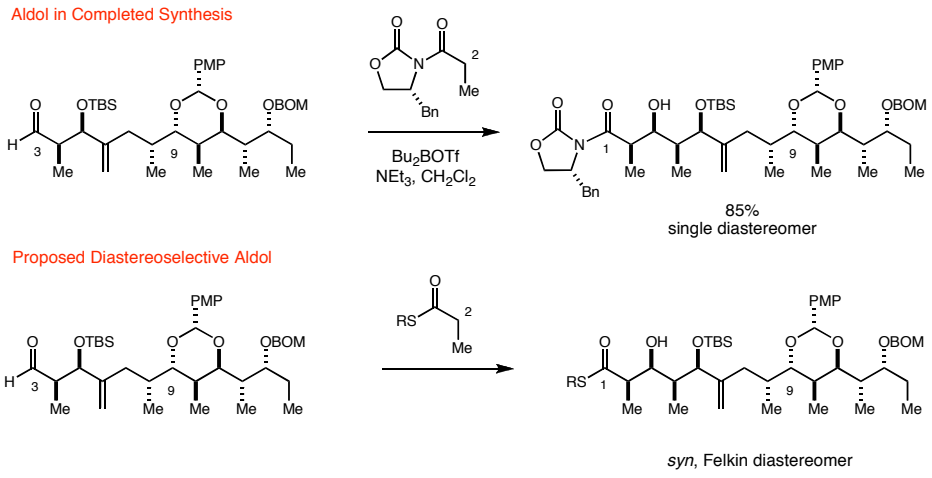
Scheme 11: Completion of the C(3)-C(15) fragment



VII. The Second Aldol Disconnection

Arguably the most difficult relative stereochemical relationship to form on the erythronolide backbone is the all *syn* stereotetrad from C(2)-C(5). In the synthesis carried out by Vy Dong, this sequence of the seco acid was forged by a highly diastereoselective aldol reaction that efficiently and selectively gave the desired adduct, but relied on Evan's chiral oxazolidinone technology to enforce the proper stereochemical outcome (Figure 4). While this stands as an impressive result and is further testimony to the utility

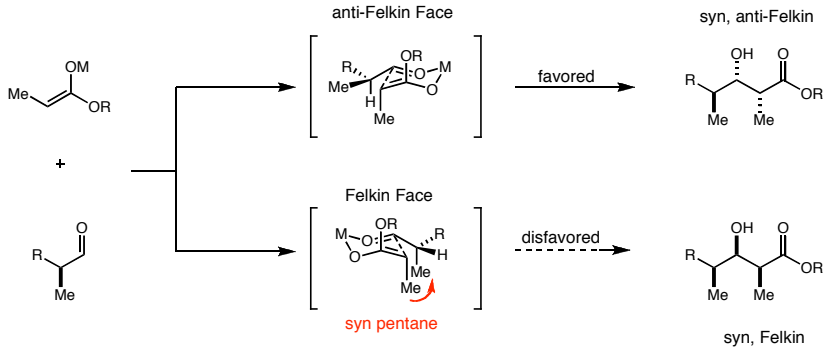
Figure 4: Proposed diastereoselective aldol



of these chiral auxiliaries in complex aldol reactions, we were curious as to whether or not we could use the inherent chirality of the aldehyde to give the desired stereochemical outcome without the use of chiral controller groups.

Analysis of the competing closed transition states illustrates that a simple diastereoselective aldol may not be straightforward. In the transition state leading to the desired product the methyl group of the nucleophile encounters a highly destabilizing *syn* pentane interaction (+3.7 kcal/mol) with the α-methyl stereocenter of the aldehyde. This

Scheme 12: Analysis of closed transition states



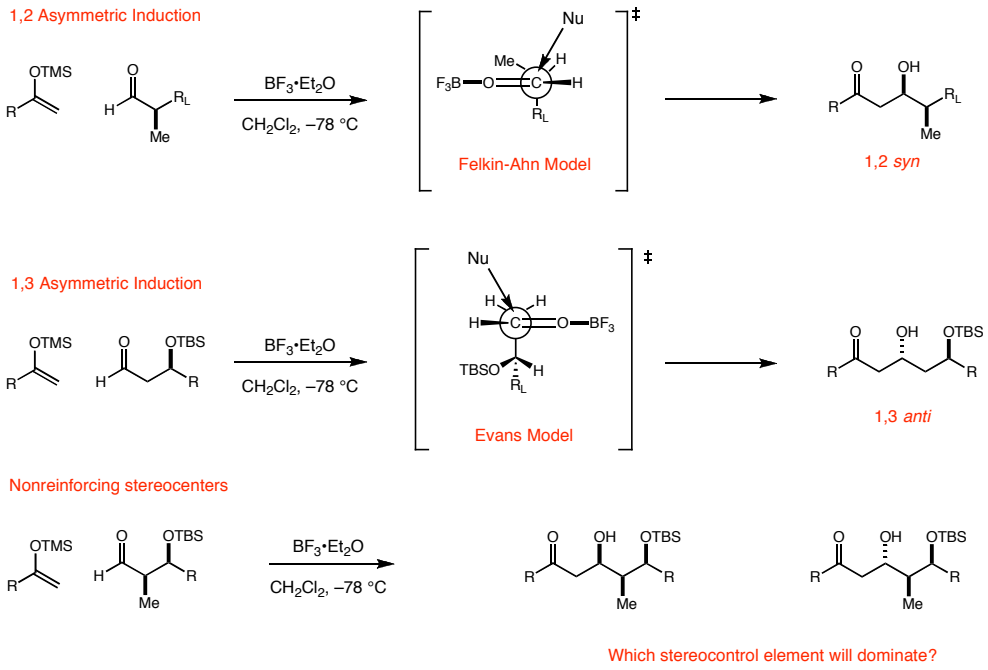
strongly disfavors the *syn*, Felkin diastereomer required for the erythronolides. Rather, this energetically costly interaction is avoided if the enolate attacks the opposite aldehyde carbonyl face, which gives rise to the favored *syn*, anti-Felkin stereochemistry, as was observed in the Woodward synthesis (Scheme 7). Thus it seemed likely that traditional closed transition state aldol chemistry would not furnish the correctly configured product.

At this juncture it was speculated that Lewis acid-mediated Mukaiyama aldol reactions might provide access to the desired stereochemical relationship. It is widely accepted that Lewis acid-promoted additions of silyl ketene acetals to aldehydes occur through open transition states. Thus it was postulated that access to diastereomers that are

disfavored by Zimmerman-Traxler chair transition states may be possible, such as the *syn*, Felkin adduct required for our synthesis.

While simple diastereoselection in Mukaiyama aldol processes is often variable, stereoselective additions to chiral aldehydes are well precedented.[12,13] However, in order to ensure successful diastereoselection the impact of each stereocenter proximal to the starting aldehyde must be understood. Evans has conducted a systematic study of ketone enolsilane additions into α,β-chiral aldehydes with a variety of relative stereochemistries and protecting groups.[14,15] These results suggest that induction afforded by the *syn* α-methyl and β-siloxy group of the aldehyde component are actually nonreinforcing

Scheme 13: Analysis of competing induction elements in open transition states



[12] Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322–4343.

[13] Heathcock, C. H.; Davidsen, S. K.; Hug, K. T.; Flippin, L. A. *J. Org. Chem.* **1986**, *51*, 3027–3037.

[14] Evans, D. A.; Dart, M. J.; Duffy, J. L.; Rieger, D. L. *J. Am. Chem. Soc.* **1995**, *117*, 9073–9074

[15] Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G.; Livingston, A. B. *J. Am. Chem. Soc.* **1995**, *117*, 6619–6620.

(Scheme 13). Additions to α-chiral aldehydes generally adopt transition state structures wherein the non-bonding interactions are minimized, giving 1,2-*syn* products (Felkin products). However, it has been found that even under nonchelating conditions β-oxygen substituents give mainly the 1,3-*anti* products due to the minimization of electrostatic dipole moments on the aldehyde and steric interactions between aldehyde and the nucleophile in the transition state.

A solution needed to be devised wherein the inherent bias of the β-substituent must be overcome and the α-methyl center would dictate the facial bias of the aldehyde addition. It has been noted that as the steric bulk of the enolsilane increases, the influence of β-oxygen substituent in biasing the transition state toward the 1,3, *anti* products is greatly diminished.[16] Thus by employing very bulky silyl ketene acetals we hoped to arrive at conditions favoring formation of the *syn*, Felkin adduct. However, it is crucial to note that all the examples Evans employs rely on ketone enolates. To the best of our knowledge there are no reports of ester oxidation state enolsilanes adding to *syn* α-methyl, β-siloxy aldehydes with uniformly high levels of stereocontrol. Furthermore, Evans proposes no model transition states for propionate nucleophiles.[17] Thus we felt that rendering this aldol reaction diastereoselective would not only represent a solution to a standing problem in the erythronolide literature but also contribute to a better understanding of related propionate silyl ketene acetal additions into α, β-chiral aldehydes in a more general sense.

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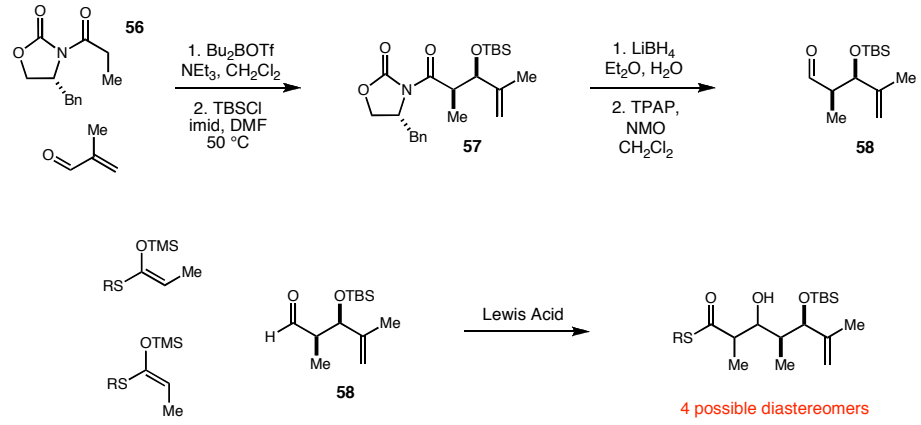
[16] Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc*. **1996**, *118*, 4322–4343.

[17] Evans, D. A.; Yang, M. G.; Dart, M. J.; Duffy, J. L.; Kim, A. S. *J. Am. Chem. Soc.* **1995**, *117*, 9598–9599.

Due to the lengthy preparatory sequence required to access meaningful amounts of the actual erythronolide intermediate, a model system was proposed that would allow optimization of reaction conditions. The synthesis is straightforward and is described below in Scheme 14.

Scheme 14: Development of model system



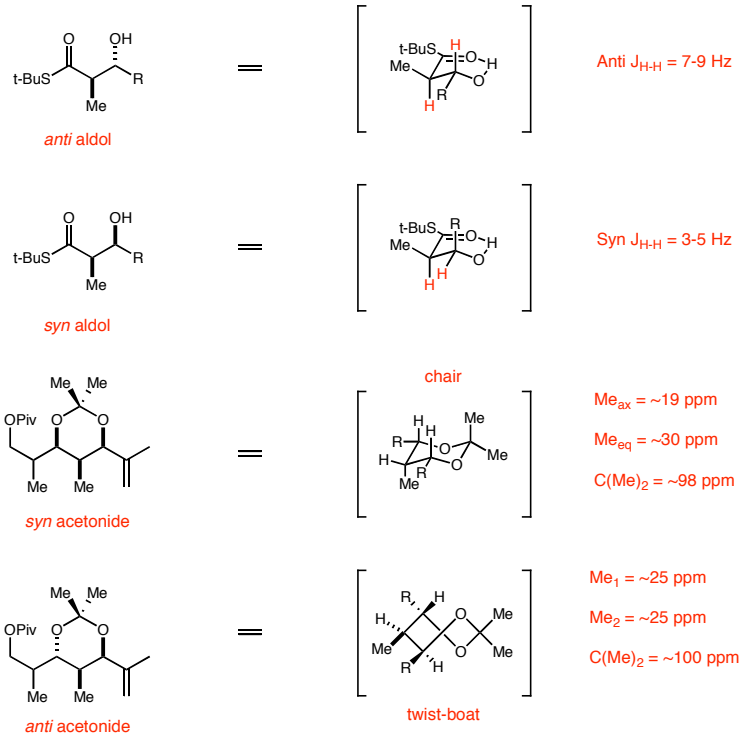
Methacrolein was condensed with the boron enolate of auxiliary **56**. This adduct was then protected as its silyl ether and the auxiliary was reductively excised. Oxidation of the resulting primary alcohol gives the known model aldehyde **58** for use in our studies. It should be noted that this aldehyde is known in the literature to be unstable to storage. As a result it was freshly oxidized from the alcohol prior to each usage.

Figure 5: Four possible diastereomeric products

From this aldehyde a range of propionate nucleophiles, solvents, and Lewis acids were investigated in the search for conditions that would give the desired stereochemical outcome. The stereochemistry of these model aldol products was established by a two-

part method. By measuring the coupling constant between the protons on the α- and β-carbons of the chain the relative stereochemistry between these two centers was assigned. After a series of steps the aldol products could be converted to their corresponding acetonides, allowing the relative 2,4-stereochemical relationship to be determined according to the method of Rychnovsky.[18] With the relative stereochemistry of the starting aldehyde known, these two pieces of NMR evidence enabled complete assignment of the relative stereochemistry for the entire chain.

Figure 6: NMR methods to assign stereochemistry of aldol products



Thioester nucleophiles were chosen due to their more selective reactivity compared to their ester enolate counterparts. In line with Evans' observations the first nucleophile examined was 1-(*tert*-butylthio)prop-1-enyloxy)trimethylsilane, in the hope

[18] Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem* **1993**, *58*, 3511–3515.

that its bulk would aid in proper diastereoselection. However, much to our surprise, both enolate geometries gave a high yields the of the *anti*, Felkin product as a single diastereomer when BF_3•Et_2O was employed as a Lewis acid in CH_2Cl_2 at –78 °C. While at first puzzling, this result was promising in that the aldehyde α-methyl center was properly directing the facial selectivity. However, the newly formed methyl center had the wrong configuration. This was later found to fall in line with Gennari's observation that the S-*t*Bu propionate nucleophiles undergo a destabilizing steric interaction between the enol methyl group and the Lewis acid in the transition state as a consequence of unusually obtuse bond angles found in this class of silyl ketene acetals.[19] Despite extensive investigations and considerable effort, all other Lewis acids and solvent combinations that were evaluated gave non-selective mixtures of diastereomers, presumably through the viability of a number of competing transition state structures.

At this point focus switched to ethyl thioester nucleophiles in the hope that they would retain enough bulk to render 1,2 induction favorable, but not so much as to maintain the negative interaction with the Lewis acid experienced by the *tert*-butyl thioester nucleophiles. However, the intermediate steric bulk of this nucleophile produced unselective mixtures of diastereomers in all solvents and with all the Lewis acids surveyed, presumably due to the intermediacy of a number of competing, viable transition states. In the end no conditions employed provided any meaningful amount of the *syn*, Felkin diastereomer.

VIII. Conclusion and Future Directions

[19] Gennari, C.; Beretta, M. G.; Bernardi, A.; Moro, G.; Scolastico, C.; Todeschini, R. *Tetrahedron* **1986**, *42*, 893–909.

After several months no conditions evaluated appeared to selectively produce the desired diastereomer and the focus of my research switched to the synthesis of diazonamide A, as is described in the earlier part of this report. As yet the *syn*, Felkin aldol problem still has no general solution. However, as synthetic organic chemistry advances and catalytic asymmetric methods capable of overriding intrinsic stereochemical preferences are developed, the prospects for the future success of this reaction seem undimmed.

Chapter 6 Supporting Information

General Information: Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[20] All solvents were purified according to the method of Grubbs.[21] Nonaqueous reagents were transferred under argon via syringe or cannula. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator using a heated water bath. Chromatographic purification of products was accomplished using forced-flow chromatography on Silicycle 230–400 mesh silica gel 60 according to the method of Still.[22] Thin-layer chromatography (TLC) was performed on Silicycle 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by fluorescence quenching or by CAM stain.

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVANCE 500 (500 MHz and 125 MHz) as noted, and are internally referenced to residual solvent signals. Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (Hz) and assignment. Data for ^{13}C NMR are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer 1000 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Mass spectra were obtained from the Caltech Mass Spectral Facility.

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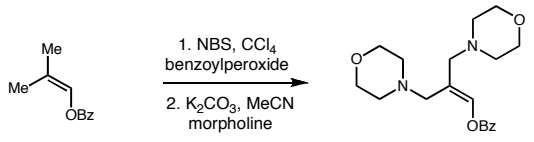
[20] Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals;* 3rd ed., Pergamon Press, Oxford, 1988.

[21] Pangborn, A. B.; Giardello, M. A,; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.

[22] Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978**, *43*, 2923.

Optical rotations were measured on a Jasco P-1010 polarimeter, and $[a]_D$ values are reported in 10^{-1} dg cm^2 g^{-1}.

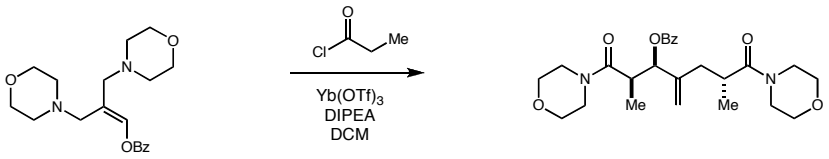
Note: All proton and carbon spectra and optical rotations were identical to those reported by Vy Dong in her Ph.D. thesis (Caltech, 2003). The HRMS and IR data for erythronolide intermediates presented here were taken from Dong's Thesis.



48 40

Benzoic acid-2-(-N-methyl-morpholinyl)-3-(-N-morpholinyl)-propenyl ester 40: To a solution of benzoic acid 2-methyl-propenyl ester (1.83 g, 10.37 mmol) and NBS (3.87 g, 21.77 mmol) in 26 mL of refluxing CCl_4 was added benzoyl peroxide (0.05 g, 0.02 mmol). After two hours the reaction the reaction mixture was filtered through Celite and concentrated *in vacuo* to give the crude dibromide that was used without further purification. The crude dibromide was taken up in acetonitrile (270 mL) containing a suspension of K_2CO_3 (4.43 g, 27 mmol). Morpholine (11.76 mL, 135 mmol) was added dropwise by syringe over several minutes and the resulting reaction mixture was stirred at room temperature for 2 hours until judged complete by TLC. Dilution with 500 mL of ether was followed by 3 x 200 mL water washes. The organic fractions were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by chromatography on alumina (100% Et_2O) furnishes the desired product as a yellow solid (3.59 g, 99%) IR (film): 1729, 1455, 1293, 1274, 1251, 1116, 1004, 865 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, 2H, J = 7.2 Hz, Ar), 7.63 (app t, 1H, J = 7.4 Hz, Ar), 7.50 (app t, 2H, J = 7.6 Hz, Ar), 7.42 (s, 1H,

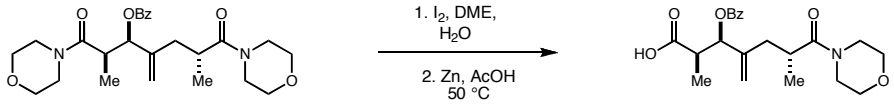
C=C**H**), 3.72–3.68 (m, 8H, 2 x O(C**H₂**)₂), 3.21 (s, 2H, **CH₂**C=C), 3.02 (s, 2H, **CH₂**C=C), 2.50–2.45 (m, 8H, 2 x N(C**H₂**)₂); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.4, 135.3, 133.7, 129.9, 129.0, 128.6, 119.4, 67.1, 58.8, 54.0, 53.8, 53.6; HRMS (FAB+) exact mass calc. for [M+H] ($C_{19}H_{27}N_2O_4$) requires *m/z* 347.1971, found *m/z* 347.1971.



49 **46**

(2R*, 3R*, 6R*)-2,6-dimethyl-4-methylene-1,7-dimorpholino-1,7-dioxoheptan-3yl-benzoate 46: A round bottom flask containing the bisallylic amine **40** (300 mg, 0.867 mmol) and a stirbar was charged with $Yb(OTf)_3$ (1.07 g, 1.73 mmol), sealed with a rubber septum, and brought out of the box. 17 mL of CH_2Cl_2 was added by syringe, followed by Hünig's base (0.65 mL, 3.46 mmol), and then propionyl chloride (3.5 mL, 3.46 mmol). The resulting solution was stirred under argon at room temperature for 6 hours. After this time 10 mL of 1 M NaOH was added, and the resulting solution was washed 3 x 100 mL with ethyl acetate and the organic portion was dried over sodium sulfate. Following concentration, the resulting oil was purified by silica gel chromatography (100% ethyl acetate) to afford the title compound as a white solid (340 mg, 86%) in a 10:1 mix of diastereomers *syn*:*anti* : *syn*:*syn.* IR (film): 2247. 1722, 1637. 1440, 1274, 1116, 1031, 703 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, 2H, J=9.0 Hz, Ar), 7.58 (t, 1H, J = 9.3 Hz, Ar), 7.45 (t, 2H, J = 9.5 Hz, Ar), 5.69 (d, 1H, J = C**H**OBz), 5.19 (s, 1H, C**H**(H)=C), 4.98 (s, 1H, C**H**(H)=C), 3.70–3.48 (br m, 16H, 2 x ($O(CH_2CH_2)_2N$)), 3.25 (dt, 1H, J = 8.5

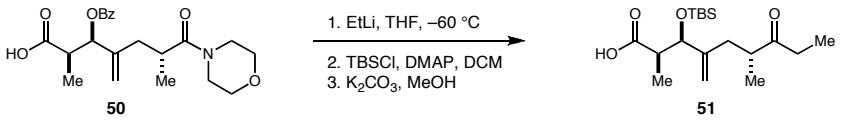
and 17.5 Hz, 1H, C**H**CHOBz), 3.02 (app t, 1H, J = 8.5 and 20.4 Hz, (CO)C**H**CH_2), 2.55 (dd, 1H, 18.0 Hz, C**H**(H)=CH_2), 2.14 (dd, 1H, 8.5 and 18.0 Hz, C**H**(H)=CH_2), 1.24 (d, 3H, J = 8.5 Hz, Me), 1.07 (d, 3H, J=8.5 Hz, Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6, 171.7, 165.3, 145.1, 133.0, 130.0, 129.5, 128.4, 114.2, 76.0, 66.8, 46.2, 45.9, 42.1, 38.8, 37.4, 33.9, 17.7, 13.8; HRMS (FAB+) exact mass calc. for [M+H] ($C_{25}H_{35}N_2O_6$) requires *m/z* 459.2495, found *m/z* 459.2481.



46 **50**

(2R*,3R*,6R*)-3-benzoate-2,6-dimethyl-4-methylene-7-morpholin-4yl-heptanoic acid 50: To a solution of bisamide **46** (420 mg, 0.915 mmol) in 4.6 mol of a DME : water solution was added iodine (511 mg, 2.013 mmol). The resulting black solution was stirred in the absence of light for three hours at room temperature at which time it was diluted with 20 mL of ethyl acetate and quenched with 10 mL of a saturated solution of $Na_2S_2O_3$. The organic phase was washed with 50 mL of brine and dried over sodium sulfate prior to concentration *in vacuo*. The resulting oil was then dissolved in 10 mL of acetic acid and zinc metal (4.39 mg, 6.72 mmol) was added. The resulting suspension was heated to 50 °C under argon for 2 hours, after which time it was cooled to room temperature and treated with 1N HCl. The crude mixture was then extracted 3 x 100 mL ethyl acetate and the combined organics were washed with brine, dried over sodium sulfate, and concentrated. The resulting crude yellow solid was pushed through a pad of silica gel with ethyl acetate, and this residue was concentrated to yield the product as a sticky white

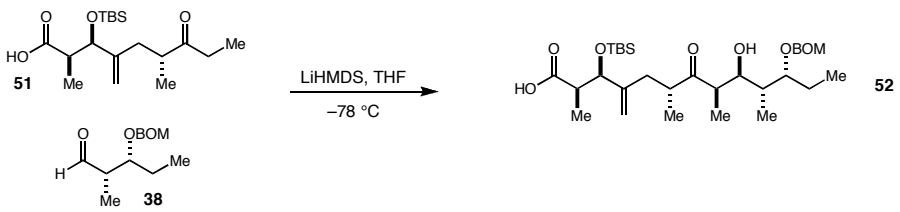
solid in an 83:17 mixture of regioisomers *α,β-disubstituted acid* : *α,β-disubstituted amide.* This mixture could be triturated with –78 °C ether to give the title compound in isomerically pure form (322 mg). IR (film): 2981, 2935, 2866, 1722, 1637, 1452, 1274, 1112, 1027, 966, 850 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, 2H, J=9.0 Hz, Ar), 7.58 (app t, 1H, J = 9.3 Hz, Ar), 7.45 (t, 2H, J = 9.5 Hz, Ar), 5.69 (d, 1H, J = C**H**OBz), 5.09 (s, 1H, C**H**(H)=C), 4.98 (s, 1H, C**H**(H)=C), 3.75–3.48 (br m, 8 H, ($O(CH_2CH_2)_2N$)), 3.05–2.99 (m, 2H 2 x C**H**CH_3), 2.61 (dd, 1H, J = 7.0 and 14.5 Hz, C**H**(H)=CH_2), 2.18 (dd, 1H, 6.5 and 15.0 Hz, C**H**(H)=CH_2), 1.28 (d, 3H, J = 7.0 Hz, Me), 1.13 (d, 3H, J=8.5 Hz, Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.8, 175.2, 165.3, 143.5, 133.2, 129.6, 128.5, 128.4, 113.9, 75.6, 66.8, 66.7, 46.1, 42.4, 41.8, 36.9, 34.0, 17.8, 10.9; HRMS (FAB+) exact mass calc. for [M+H] ($C_{21}H_{27}NO_6$) requires *m/z* 389.1838, found *m/z* 389.1845.



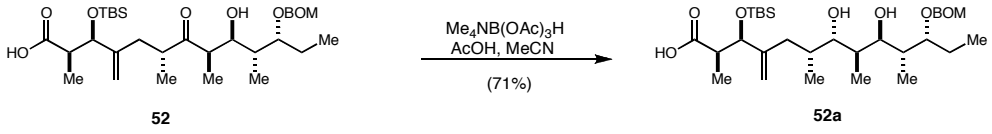
50 **51**

(2R*,3R*,6R*)-3-(*tert*-butyl-dimethyl-silanoxy)-2,6-dimethyl-4-methylene-7-oxo-nonanoic acid 51: To a solution of acid **50** (910 mg, 2.34 mmol) in 20 mL of THF at –63 °C was added freshly prepared ethyl lithium (14.73 mmol) by syringe pump over 30 minutes as 0.6 M solution in diethyl ether. After 1 hour the reaction mixture was quenched with 50 mL of NH_4Cl and 50 mL of 1 M $KHSO_4$ and allowed to warm to room temperature. The aqueous layer was extracted with 3 x 100 mL of ethyl acetate and dried over sodium sulfate prior to concentration. The resulting ketone was used without further purification. A solution of TBSCl (2.31 g, 15.33 mmol) and imidazole (2.08 g, 30.66

mmol) in 8 mL of DMF was added to the ethyl ketone via cannula under an argon atmosphere. After 16 hours at room temperature the reaction mixture was diluted with 50 mL of $KHSO_4$ and extracted 3 x 50 mL with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The resulting bis silyl ether was taken up in a 0.25M solution of K_2CO_3 in MeOH (45 mL) and stirred for 30 minutes, after which time the reaction mixture was diluted with 50 mL of $KHSO_4$ and the methanol was removed *in vacuo*. The remaining aqueous suspension was extracted 3 x 100 mL with ethyl acetate, dried over sodium sulfate, concentrated, and purified by silica gel chromatography (20% ethyl acetate in hexanes) to afford the title compound as a clear oil in 54% yield over the three steps. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.16 (s, 1H, C=C(**H**)H), 4.89 (s, 1H, C=C(**H**)H), 4.46 (d, 1H, J = 4.8 Hz, C**H**OTBS), 2.9–2.75 (m, 1H), 2.70–2.60 (m, 1H), 2.60–2.45 (m, 1H), 2.48 (q, 2H, J =7.2 Hz, C**H$_2$**CH_3), 2.38 (dd, 1H, J = 7.2 and 15.3 Hz, CH(**H**)C=CH_2), 2.01 (dd, 1H, J = 7.4 and 15.8 Hz, CH(**H**)C=CH_2), 1.13 (d, 3H, J =7.2 Hz, Me), 1.10 (d, 3H, J =7.8 Hz, Me), 1.07 (t, 3H, J = 7.2 Hz, CH_2C**H$_3$**), 0.91 (s, 9H, TBS), 0.06 (s, 3H, TBS), 0.00 (s, 3H, TBS); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.5, 179, 146.5, 113.1, 76.3, 44.4, 44.0, 34.5, 34.4, 26.1, 18.4, 17.3, 10.6, 8.1, -4.1, -5.0; HRMS (FAB+) exact mass calc. for [M+H] ($C_{18}H_{35}O_4Si$) requires *m/z* 343.2305, found *m/z* 343.2301.

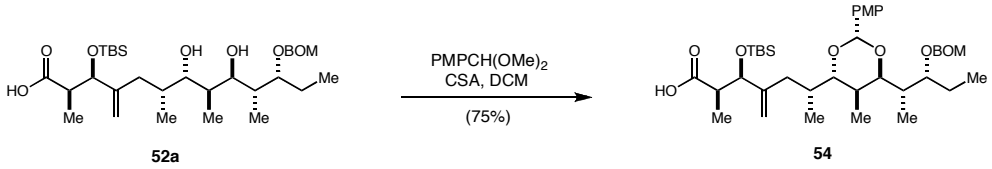


Carboxylic Acid 52: A 2.1 M solution of *n*-BuLi in hexanes (1.75 mL, 3.65 mmol) was added dropwise to a solution of freshly distilled hexamethyldisilazide (641 mg, 4.38 mmol) in 5.5 mL of THF under argon at 0 °C. After 30 minutes the reaction mixture was cooled to –78 °C and racemic ethyl ketone **51** (500 mg, 1.46 mmol) wass added in 4 mL of THF. After 120 minutes the enantiopure aldehyde **38** (780 mg, 3.31 mmol) was added dropwise in 4 mL of a –78 °C solution of THF. After 5 hours the reaction mixture was diluted with THF and quenched by the addition of 50 mL of saturated NH_4Cl solution. The organic fraction was washed with 3 x 75 mL of ethyl acetate, followed by washing with brine and drying over sodium sulfate. Concentration yielded the product acid as an inseparable mixture of diastereomers in 91% yield (760 mg, 7:7:1:1 *syn*:*syn*:*anti*:*anti*). This material was pushed through a silica plug with ethyl acetate, concentrated, and used without further purification.



Diol 52a: In a flame-dried 25 mL flask charged with $Me_4NB(OAc)_3H$ (2.42 g, 9.22 mmol) was added 10 mL of MeCN. 9 mL of anhydrous acetic acid was added and the resulting solution was cooled to –40 °C. The carboxylic acid (760 mg, 1.317 mmol) was then added in 10 mL of MeCN and the reaction was stirred at –40 °C for 8 hours. It was

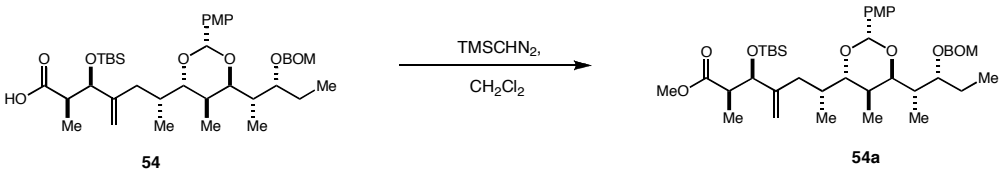
then warmed to –20 °C and stirred for 10 hours before being warmed to 0 °C for one hour. The reaction mixture was poured into 200 mL of saturated $NaHCO_3$, extracted with three 100 mL portions of ethyl acetate, dried over sodium sulfate and concentrated to yield the desired *anti* diols as a 1:1 mixture of diastereomers in 71% yield (538 mg). This material was used without further purification.



52a 54

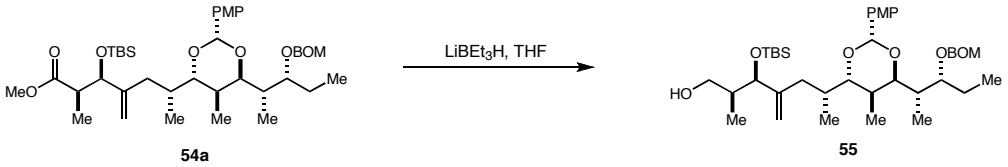
Carboxylic Acid 54: To a solution of the diol diastereomers (649 mg, 0.929 mmol) in 9.5 mL of dichloromethane under argon was added anisaldehyde dimethylacetal (0.475 mL, 2.78 mmol) and CSA (10 mg, 0.046 mmol). After 6 hours the reaction was quenched with Hünig's base (0.2 mL) and concentrated *in vacuo*. The resulting foam was purified on silica gel (10%–20 % ethyl acetate in hexanes) to yield two diastereomeric acetals in combined yield of 540 mg. *Desired Isomer*: IR (film): 3500–2600 br, 1710, 1517, 1463, 1248, 1042, 834 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, 2H, J = 8.4 Hz, Ar), 7.30–7.23 (m, 5H, Ph), 6.85 (d, 2H, J =8.1 Hz, Ar), 5.54 (s, 1H, PMPC**H**), 5.18 (s, 1H, C=C**H**(H)), 4.93 (s, 1H, C=C**H**(H)), 4.79 (dd, 2H, J = 6.6 and 11.7 Hz, OC$\mathbf{H_2}$O), 4.63 (d, 2H, J = 2.1 Hz, PhC$\mathbf{H_2}$), 4.48 (d, 1H, J = 3.9 Hz, C**H**OTBS), 4.03–3.95 (m, 2H, C**H**OPMB), 3.78 (s, 3H, ArO**Me**), 3.37 (d, 1H, J = 10.5 Hz, C**H**OBOM), 2.60–2.50 (m, 2H), 2.07 (d, 1H, J =14.7 Hz), 1.80–1.70 (m, 4H), 1.48 (dq, 1H, J = 7.3 and 21.5 Hz), 1.19 (d, 3H, J = 7.2 Hz, **Me** C(10)), 1.09 (d, 3H, J = 7.2 Hz, **Me** C(8)), 1.08 (d, 3H, J = 6.6 Hz, **Me** C(6)), 0.87 (s, 9H, TBS), 0.90-0.86 (m, 3H, CH_2**Me**), 0.82 (d, 3H, J = 6.6

Hz, **Me** C(5)), 0.02 (s, 3H, TBS), -0.01 (s, 3H, TBS); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.9, 159.7, 146.3, 138.1, 131.9, 128.5, 127.8, 127.6, 127.4, 127.3, 113.7, 95.4, 84.8, 78.5, 75.5, 75.4, 69.4, 55.5, 44.1, 37.2, 37.0, 29.9, 29.7, 29.6, 26.1, 25.9, 18.4, 16.2, 13.5, 10.9, 10.4, 7.6, -4.0, -4.8; HRMS (ES) exact mass calc. for [M+H] ($C_{40}H_{62}O_8SiNa$) requires *m/z* 721.4112, found *m/z* 721.4103; $[\alpha]_D$ = –11.1 (c = 1.0, $CHCl_3$); TLC R_f = 0.15 (20% ethyl acetate in hexanes); *Diastereomer*: $[\alpha]_D$ = –7.0 (c = 1.0, $CHCl_3$); TLC R_f = 0.20 (20% ethyl acetate in hexanes).



Methyl ester 54a: To a solution of carboxylic acid **54** (170 mg, 0.243 mmol) in 7.0 mL of CH_2Cl_2 and 0.7 mL of MeOH was added $TMSCH_2N_2$ (2.0M in ether, 0.85 mL, 1.7 mmol) at room temperature. After one hour the reaction was cooled to 0 °C and quenched by the addition of 1 mL of acetic acid. The reaction mixture was poured into 20 mL of saturated $NaHCO_3$ solution and extracted with 3 x 50 mL portions of ethyl acetate. The resulting oil was dried over sodium sulfate, concentrated, and flashed on silica gel (20 % ethyl acetate in hexanes) to yield 142 mg of the desired methyl ester. IR (film): 2931, 2361, 2339, 1735, 1616, 1518, 1457, 1250cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, 2H, J = 8.1 Hz, Ar), 7.27–7.20 (m, 5H, Ph), 6.85 (d, 2H, J =8.7 Hz, Ar), 5.53 (s, 1H, PMPC**H**), 5.14 (s, 1H, C=C**H**(H)), 4.90 (s, 1H, C=C**H**(H)), 4.79 (dd, 2H, J = 6.6 and 18.6 Hz, OC**H$_2$**O), 4.63 (dd, 2H, J = 11.9 and 20.0 Hz, PhC**H$_2$**), 4.42 (d, 1H, J = 5.1 Hz,

C**H**OTBS), 4.02–3.95 (m, 2H), 3.78 (s, 3H, ArO**Me**), 3.62 (s, 3H, CO_2**Me**), 3.37 (d, 1H, J = 10.5 Hz, C**H**OBOM), 2.50–2.40 (m, 2H), 2.07 (d, 1H, J =14.7 Hz), 1.85–1.65 (m, 4H), 1.49 (dq, 1H, J = 7.2 and 21.8 Hz), 1.20 (d, 3H, J = 6.6 Hz, **Me**), 1.09 (d, 3H, J = 6.6 Hz, **Me**), 0.97 (d, 3H, J = 6.6 Hz, **Me**), 0.87 (s, 9H, TBS), 0.92-0.86 (m, 3H, CH_2**Me**), 0.82 (d, 3H, J = 7.2 Hz, **Me**), -0.01 (s, 3H, TBS), -0.02 (s, 3H, TBS); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.7, 159.7, 146.6, 138.1, 131.9, 128.5, 127.7, 127.3, 113.7, 113.5, 95.4, 95.3, 84.8, 78.6, 76.0, 75.4, 69.7, 55.5, 51.8, 44.4, 37.2, 36.8, 30.0, 29.6, 26.0, 25.9, 18.4, 16.0, 13.6, 10.9, 10.8, 7.5, -4.0, -4.9; HRMS (ES) exact mass calc. for [M+] ($C_{41}H_{64}O_8Si$) requires *m/z* 712.4371, found *m/z* 712.4370; $[\alpha]_D$ = –7.2 (c = 1.0, $CHCl_3$).

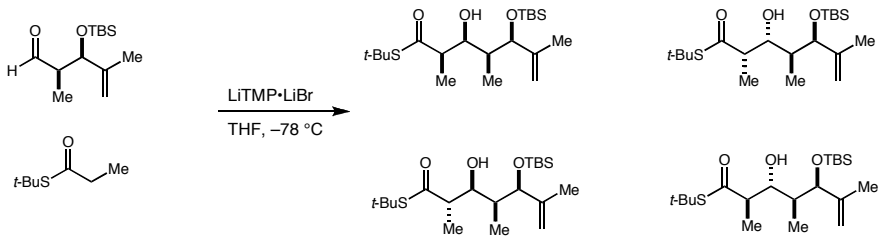


54a **55**

Alcohol 55: To a solution of ester **54a** (60 mg, 0.084 mmol) in 33 mL of THF at 0 °C was added $LiBEt_3H$ (0.336 mL, 0.336 mmol) as a 1.0 M solution in THF under argon. After 1 hour the reaction mixture was diluted with a solution $KHSO_4$ and extracted with three portions 20 mL of ethyl acetate. The combined organic layers were washed with brine and dried over sodium sulfate prior to concentration. Purification of the crude resulting oil on silica gel (25% ethyl acetate in hexanes) provided the title compound as a colorless oil in 80% yield. IR (film): 3507, 2960, 2881, 1616, 1517, 1456, 1250, 1103, 1046, 831, 776cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (d, 2H, J = 9.0 Hz, Ar), 7.30–7.25 (m, 5H, Ph), 6.84 (d, 2H, J = 8.7 Hz, Ar), 5.54 (s, 1H, PMPC**H**), 5.17 (s, 1H, C=C**H**(H)), 4.93 (s, 1H, C=C**H**(H)), 4.79 (dd, 2H, J = 6.6 and 19.8 Hz, OC**H$_2$**O), 4.61 (s,

2H, PhC**H$_2$**), 4.36 (app s, 1H, C**H**OTBS), 4.06 (d, 1H J = 10.5 Hz), 3.97 (t, 1H, J = 7.2 Hz), 3.78 (s, 3H, ArO**Me**), 3.52 (d, 2H, J = 7.2 Hz, C**H$_2$**OH), 3.36 (d, 1H, J = 11.1 Hz, C**H**OBOM), 2.60–2.45 (m, 1H), 2.13 (d, 1H, J =14.1 Hz), 1.85–1.65 (m, 1H), 1.48 (dq, 1H, J = 7.2 and 21.5 Hz), 1.19 (d, 3H, J = 6.3 Hz, **Me**), 0.98 (d, 3H, J = 6.0 Hz, **Me),** 0.87 (s, 9H, TBS), 0.92–0.88 (m, 3H, CH_2**Me**), 0.82 (d, 3H, J = 6.6 Hz, **Me**), 0.75 (d, 3H, J = 7.2 Hz, **Me**), 0.07 (s, 3H, TBS), 0.01 (s, 3H, TBS); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.8, 147.3, 137.9, 131.9, 128.5, 127.8, 127.7, 127.3, 113.7, 112.7, 95.3, 95.0, 84.9, 78.3, 75.0, 72.5, 70.0, 65.4, 55.6, 39.6, 38.6, 36.9, 29.3, 29.0, 26.3, 25.5, 18.6, 15.9, 13.3, 10.8, 9.8, 7.5, -4.0, -4.7; HRMS (ES) exact mass calc. for [M+H] ($C_{40}H_{64}O_7Si$) requires *m/z* 684.4421, found *m/z* 684.4450; $[\alpha]_D$ = –16.5 (c = 1.0, $CHCl_3$).

Model System Aldol Product Characterization and Derivatization:



General Procedure A: To a solution TMP•HBr (2.1 eq) and 1,10 phenanthroline (trace) in THF at 0 °C was added a solution of *n*-BuLi (2.0 eq) until the solution turned bright red, at which point another equal portion of *n*-BuLi (2.0 eq) was added dropwise. This solution was cooled to –78 °C and the thioester was added dropwise (2.0 eq) in a solution of THF. After an hour the aldehyde (1.0 eq) was added in a cold solution of THF. The resulting mixture was allowed to stir for 2 hours at –78 °C before being quenched by the addition of saturated ammonium chloride solution. The resulting heterogeneous solution

was allowed to warm to room temperature. It was then diluted with ethyl acetate, washed with water and brine, concentrated, and purified on silica gel.

General Procedure B: A 0.1 M solution of silyl ketene thioacetal (1.1 eq) and aldehyde (1.0) was cooled to –78 °C and Lewis acid was added dropwise (1.0 eq). After 30 minutes the resulting mixture was quenched by the addition of saturated ammonium chloride. The resulting solution was allowed to warm to room temperature. It was then diluted with ethyl acetate and washed with water and brine, concentrated, and purified on silica gel.

Diastereomer 1: IR (Film): 3515, 2957, 2928, 2857, 1657, 1472, 1456, 1364, 1252, 1135, 1042, 1019, 963, 939, 900, 874, 834, 775, 673 cm^{-1}; ^{1}H NMR: (300 MHz, $CDCl_3$) δ 4.99 (S, 1H, C=C(**H**)H), 4.88 (s, 1H, C=C(**H**)H), 4.48 (app s, 1H, C**H**OTBS), 3.38 (dt, 1H, J = 3 and 9 Hz, C**H**OH), 3.09 (d, 1H, J = 3.3 Hz, O**H**) 2.81 (dq, 1H, J_{Me-H} = 6.9 Hz and J_{H-H} = 3.0 Hz), 1.66 (m, 1H, TBSOCHC**H**(Me)CHOH), 1.64 (s, 3H, CH_2=C(**Me**)), 1.45 (s, 9H, S*t*-Bu), 1.32 (d, 1H, J = 6.9 Hz, C**H**(Me)), 0.90 (s, 9H, TBS), 0.81 (d, 1H, J = 6.9 Hz, C**H**(Me)), 0.09 (s, 3H, TBS), 0.00 (s, 3H, TBS); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 204.2, 146.4, 111.4 76.6, 74.5, 49.9, 48.7, 41.3, 29.9, 26.2, 20.1, 18.5, 16.9, 10.0, -4.2, -5.0 HRMS (FAB+) exact mass calc. for [M+H] ($C_{20}H_{41}O_5SiS$) requires *m/z* 389.2546, found *m/z* 389.2555; $[\alpha]_D$ = –34.51 (c = 0.68, $CHCl_3$).

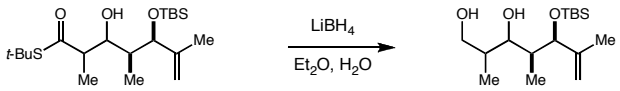
Diastereomer 2: ^{1}H NMR: (300 MHz, $CDCl_3$) δ 5.06 (S, 1H, C=C(**H**)H), 4.91 (s, 1H, C=C(**H**)H), 4.48 (app s, 1H, C**H**OTBS), 3.38 (dt, 1H, J = 3 and 8.4 Hz, C**H**OH), 2.99 (d,

1H, J = 3 Hz, O**H**) 2.71 (dq, 1H, J_{Me-H} = 6.9 Hz and J_{H-H} = 3.0 Hz), 1.67 (s, 3H, CH_2=C(**Me**)), 1.60 (m, 1H, TBSOCHC**H**(Me)CHOH), 1.47 (s, 9H, S*t*-Bu), 1.32 (d, 1H, J = 6.9 Hz, C**H**(Me)), 0.92 (s, 9H, TBS), 0.73 (d, 1H, J = 6.9 Hz, C**H**(Me)), 0.09 (s, 3H, TBS), 0.00 (s, 3H, TBS); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 206.1, 146.2, 111.6 74.5, 73.2, 50.9, 48.3, 38.8, 30.0, 26.2, 20.3, 18.5, 10.5, 9.5, -4.2, -5.0.

Diastereomer 3: IR (Film): 3532, 3072, 2958, 2928, 2885, 2857, 1769, 1678, 1472, 1461, 1455, 1364, 1251, 1217, 1161, 1117, 1067, 1005, 958, 902, 876, 837, 775; ^{1}H NMR: (300 MHz, $CDCl_3$) δ 4.93 (S, 1H, C=C(**H**)H), 4.88 (s, 1H, C=C(**H**)H), 4.04 (d, 1H, J = 7.5 Hz, C**H**OTBS), 3.72 (m, 1H, C**H**OH), 2.70 (dq, 1H, J_{Me-H} = 6.9 Hz and J_{H-H} = 8.7 Hz), 2.28 (d, 1H, J = 5.7 Hz, O**H**), 1.70–1.60 (m, 1H, TBSOCHC**H**(Me)CHOH), 1.65 (s, 3H, CH_2=C(**Me**)), 1.45 (s, 9H, S*t*-Bu), 1.09 (d, 1H, J = 7.2 Hz, C**H**(Me)), 0.91 (d, 1H, J = 6.9 Hz, C**H**(Me)), 0.89 (s, 9H, TBS), 0.052 (s, 3H, TBS), -0.007 (s, 3H, TBS); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 205.0, 146.1, 113.5, 79.8, 74.0, 52.4, 48.4, 38.6, 30.0, 26.2, 26.1, 26.0, 18.4, 17.6, 15.4, 8.3, -4.3, -4.9; HRMS (FAB+) exact mass calc. for [M+H] ($C_{20}H_{41}O_5SiS$) requires *m/z* 389.2546, found *m/z* 389.2562; $[\alpha]_D$ = 31.48 (c = 1.0, $CHCl_3$).

Diastereomer 4: IR (Film): 3527, 2958, 2929, 2858, 1678, 1456, 1364, 1256, 1067, 958, 902, 876, 836, 774, 674 cm^{-1}; ^{1}H NMR: (300 MHz, $CDCl_3$) δ 4.92 (S, 1H, C=C(**H**)H), 4.89 (s, 1H, C=C(**H**)H), 4.04 (d, 1H, J = 5.1 Hz, C**H**OTBS), 3.76 (m, 1H, C**H**OH), 2.71 (dq, 1H, J_{Me-H} = 6.9 Hz and J_{H-H} = 9.0 Hz), 2.40 (d, 1H, J = 3.3 Hz, O**H**), 1.72 (m, 1H, TBSOCHC**H**(Me)CHOH), 1.61 (s, 3H, CH_2=C(**Me**)), 1.45 (s, 9H, S*t*-Bu), 1.23 (d, 1H, J

= 6.9 Hz, C**H**(Me)), 0.91 (d, 1H, J = 6.0 Hz, C**H**(Me)), 0.90 (s, 9H, TBS), 0.09 (s, 3H, TBS), 0.00 (s, 3H, TBS); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 203.7, 145.9, 112.6, 80.5, 75.4, 52.8, 48.2, 38.6, 29.9, 26.1, 18.5, 18.3, 15.3, 7.2, -4.2, -4.9; HRMS (FAB+) exact mass calc. for [M+H] ($C_{20}H_{41}O_5SiS$) requires *m/z* 389.2546, found *m/z* 389.2556; $[\alpha]_D$ = –4.36 (c = 1.0, $CHCl_3$).



General Procedure: To a solution of thioester (1.0 eq) at 0 °C in ether (0.15 M) was added $LiBH_4$ as a 2.0 M solution in THF. After 3 hours the reaction mixture was quenched by the addition of aqueous Rochelle's salt, extracted with ether and dried over sodium sulfate. Following concentration, the resulting oil could be purified on silica gel.

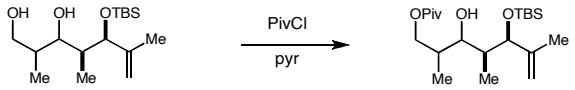
Diastereomer 1 diol: ^{1}H NMR: (300 MHz, $CDCl_3$) δ 4.95 (app s, 2H), 4.38 (d, 1H, J = 2.4 Hz), 3.85 (dd, 1H, J = 3.6 and 10.8 Hz), 3.60 (m, 2H), 3.41 (br m, 2H), 1.95–1.80 (m, 2H), 1.72 (s, 3H), 1.02 (d, 3H, J = 7.2 Hz), 0.90 (s, 9H), 0.86 (d, 1H, J = 7.2 Hz), 0.11 (s, 3H), 0.02 (s, 3H); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 145.1, 113.0, 80.8, 77.9, 66.5, 39.4, 36.6, 26.1, 26.0, 20.3, 18.3, 15.0, 12.0, -4.1, -4.8; HRMS (FAB+) exact mass calc. for [M+H] ($C_{20}H_{41}O_5SiS$) requires *m/z* 303.2536, found *m/z* 303.2359; $[\alpha]_D$ = –23.6 (c = 4.76, $CHCl_3$).

Diastereomer 2 diol: ^{1}H NMR: (300 MHz, $CDCl_3$) δ 4.95 (app s, 2H), 4.30 (d, 1H, J = 3.3 Hz), 3.90–3.60 (m, 4H), 1.55–1.60 (m, 2H), 1.77 (s, 3H), 0.95 (d, 3H, J = 6.9 Hz),

0.91 (s, 9H), 0.90 (d, 1H, J = 6.9 Hz), 0.09 (s, 3H), 0.02 (s, 3H); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 145.5, 113.0, 79.1, 75.9, 68.5, 40.6, 36.4, 26.0, 20.3, 18.4, 12.0, 8.6, -4.6, -5.2.

Diastereomer 3 diol: IR (Film): 3368, 3073, 2957, 2929, 2857, 2884, 2359, 2342, 1652, 1472, 1462, 1251, 1071, 1053, 971, 901, 875, 836, 774, 675 cm^{-1}; ^{1}H NMR: (300 MHz, $CDCl_3$) δ 4.96 (S, 1H, C=C(**H**)H), 4.91 (s, 1H, C=C(**H**)H), 4.08 (d, 1H, J = 7.5 Hz, C**H**OTBS), 3.65 (br d, 2H, J = 5.4 Hz), 3.55 (d, 1H, J = 9.6 Hz), 3.33 (br s, 1H), 1.90–1.70 (m, 3H), 1.66 (s, 3H, CH_2=C(**Me**)),0.90 (s, 9H, TBS), 0.89 (d, 1H, J = 6.6 Hz, C**H**(Me)), 0.75 (d, 1H, J = 6.9 Hz, C**H**(Me)), 0.087 (s, 3H, TBS), 0.005 (s, 3H, TBS); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 146.0, 112.8, 81.0, 80.2, 69.2, 38.3, 37.8, 26.1, 18.6, 18.3, 13.8, 7.0, -4.3, -5.0; HRMS (FAB+) exact mass calc. for [M+H] ($C_{16}H_{35}O_5Si$) requires *m/z* 303.2356, found *m/z* 303.2341; $[\alpha]_D$ = 7.41 (c = 3.36, $CHCl_3$).

Diastereomer 4 diol: IR (Film): 3363, 3069, 2927, 2955, 2885, 2857, 1471, 1461, 1377, 1249, 1140, 1067, 1051, 1034, 968, 895, 877, 836, 775, 679, 550 cm^{-1}; ^{1}H NMR: (300 MHz, $CDCl_3$) δ 4.96 (S, 1H, C=C(**H**)H), 4.90 (s, 1H, C=C(**H**)H), 4.04 (d, 1H, J = 5.1 Hz, C**H**OTBS), 3.70–3.60 (m, 3H), 2.04 (br s, 2H), 1.86 (m, 1H), 1.78 (m, 1H) 1.67 (s, 3H, CH_2=C(**Me**)), 1.03 (d, 1H, J = 6.9 Hz, C**H**(Me)), 0.92 (d, 1H, J = 6.9 Hz, C**H**(Me)), 0.91 (s, 9H, TBS), 0.06 (s, 3H, TBS), 0.00 (s, 3H, TBS); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 146.0, 112.5, 79.7, 76.0, 66.9, 38.8, 38.5, 26.1, 18.9, 18,4, 12.5, 8.2, -4.2, -4.9; HRMS (FAB+) exact mass calc. for [M+H] ($C_{16}H_{35}O_5Si$) requires *m/z* 303.2356, found *m/z* 303.2367; $[\alpha]_D$ = 15.83 (c = 1.43, $CHCl_3$).



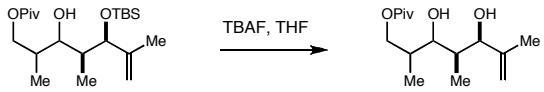
General Procedure: To a solution of diol (1.0 eq) in pyridine (0.1 M) is added PivCl (2.0 eq). After 1 hour the resulting solution was diluted with toluene and concentrated. The crude reaction mixture was loaded directly onto silica gel and chromatographed to yield the product alcohol.

Diastereomer 2 Pivoate: ^{1}H NMR: (300 MHz, $CDCl_3$) 4.96 (s, 1H), 4.93 (s, 1H), 4.37 (d, 1H, J = 2.4 Hz), 4.16 (dd, 1H, J = 8.4 and 10.8 Hz), 3.96 (dd, 1H, J = 6.0 and 10.8 Hz), 3.59 (d, 1H, J = 9.9 Hz), 3.03 (br s, 1H), 2.00–1.88 (m, 1H), 1.80–1.70 (m, 1H), 1.73 (s, 3H), 1.20 (s, 9H), 0.87 (d, 3H J = 6.9 Hz), 0.71 (d, 3H, J = 7.2 Hz), 0.06 (s, 3H), 0.003 (s, 3H); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 179.1, 145.9, 112.4, 71.7, 67.4, 39.9, 39.0, 35.1, 27.4, 26.7, 26.1, 20.3, 18.4, 11.0, 8.8, -4.5, -5.0.

Diastereomer 3 Piovate: IR (Film): 3523, 3072, 2959, 2930, 2883, 2857, 2359, 2340, 1730, 1712, 1480, 1472, 1462, 1286, 1251, 1168, 1070, 975, 877, 836, 774, 679 cm^{-1}; ^{1}H NMR: (300 MHz, $CDCl_3$) δ 4.93 (s, 1H), 4.85 (s, 1H), 4.39 (dd, 1H, J = 4.8 and 10.8 Hz), 4.03 (m, 1H), 3.47 (app q, 1H, J = 7.2 Hz), 3.26 (m, 1H), 2.63 (d, 1H, J = 3.9 Hz), 1.90-1.80 (m, 1H), 1.75–1.65 (m, 1H), 1.64 (s, 3H), 1.19 (s, 9H), 0.91 (d, 3H, J = 3.0 Hz), 0.89 (s, 9H), 0.87 (d, 3H, J = 6.6 Hz), 0.067 (s, 3H), 0.00 (s, 3H); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 184.3, 151.2, 118.0, 85.7, 77.7, 71.8, 44.0, 42.7, 41.9, 32.3, 31.6, 31.0, 23.3, 22.5, 18.9,

12.5, 0.55, 0.00; HRMS (FAB+) exact mass calc. for [M+H] ($C_{21}H_{43}O_4Si$) requires *m/z* 387.2931, found *m/z* 387.2927; $[\alpha]_D$ = 7.01 (c = 3.36, $CHCl_3$).

Diasteromer 4 Pivoate: IR (Film): 3533, 2958, 2930, 2884, 2857, 2360, 1731, 1713, 1481, 1473, 1462, 1398, 1388, 1369, 1285, 1251, 1161, 1069, 974, 939, 900, 876, 836, 774, 676 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ 4.95 (S, 1H, C=C(**H**)H), 4.89 (s, 1H, C=C(**H**)H), 4.10–4.00 (m, 2H), 3.92–3.84 (m, 1H), 3.49 (m, 1H), 2.2 (d, 1H, J = 3.9 Hz), 1.96 (m, 1H), 1.76 (m, 1H), 1.65 (s, 3H, CH_2=C(**Me**)), 1.19 (s, 9H, Piv), 1.04 (d, 1H, J = 6.9 Hz, Me), 0.91 (d, 1H, J = 5.4 Hz, Me), 0.90 (s, 9H, TBS), 0.07 (s, 3H, TBS), 0.00 (s, 3H, TBS); ^{13}C NMR: (75 MHz, $CDCl_3$) 183.7, 151.0, 117.6, 85.4, 80.0, 71.9, 44.0, 43.6, 41.5, 32.4, 31.7, 31.0, 23.5, 23.3, 18.9, 12.7, 0.7, 0.0; HRMS (FAB+) exact mass calc. for [M+H] ($C_{21}H_{43}O_4Si$) requires *m/z* 387.2931, found *m/z* 387.2931; $[\alpha]_D$ = 12.83 (c = 1.0, $CHCl_3$).



General Procedure: To a solution of alcohol (1.0 eq) in THF (0.1 M) was added TBAF (2.0 eq) as a 1.0 M solution in THF. After ten minutes the reaction was judged complete and the reaction was concentrated and pushed through a silica plug. The product was used without further purification.

General Procedure: To a solution of diol (1.0 eq) in 2,2-DMP (0.1 M) was added CSA (trace). After ten minutes the reaction was judged complete and the reaction was concentrated and purified on silica gel.

Diastereomer 2 Acetonide: ^{1}H NMR: (300 MHz, $CDCl_3$) δ 4.99 (S, 1H, C=C(**H**)H), 4.86 (s, 1H, C=C(**H**)H), 4.16 (app d, 1H, J = 1.8 Hz, C=CC**H**OC(Me)$_2$), 4.00 (m, 2H, C**H$_2$**OPiv), 3.51 (dd, 2H, J = 2.7 and 8.4 Hz, C**H**OC(Me)$_2$), 2.00–1.85 (m, 2H), 1.66 (s, 3H, C=C**Me**), 1.32 (s, 3H, acetonides **Me**), 1.30 (s, 3H, acetonides **Me**), 1.20 (s, 9H, Piv), 0.97 (d, 3H, J = 6.9 Hz, **Me**), 0.69 (d, 3H, J = 6.9 Hz, **Me**); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 145.5, 110.3, 100.9, 74.0, 71.9, 66.5, 36.0, 35.5, 27.4, 25.2, 23.7, 20.2, 12.5, 11.1.

Diastereomer 3 Acetonide: IR (Film): 2972, 2938, 2876, 1729, 1480, 1459, 1380, 1284, 1259, 1202, 1159, 1104, 1018, 998, 976, 935, 901, 869, 770 cm^{-1}; ^{1}H NMR: (300 MHz, $CDCl_3$) δ 5.04 (S, 1H, C=C(**H**)H), 4.90 (s, 1H, C=C(**H**)H), 4.26 (app s, 1H, C=CC**H**OC(Me)$_2$), 4.11 (m, 2H, C**H$_2$**OPiv), 3.70 (dd, 2H, J = 2.4 and 9.6 Hz, C**H**OC(Me)$_2$), 2.00–1.85 (m, 1H), 1.67 (s, 3H, C=C**Me**), 1.70–1.60 (m, 1H), 1.41 (s, 3H, acetonides **Me**), 1.39 (s, 3H, acetonides **Me**), 1.21 (s, 9H, Piv), 0.90 (d, 3H, J = 6.9 Hz, **Me**), 0.73 (d, 3H, J = 6.9 Hz, **Me**); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 178.8, 142.9, 110.6, 99.1, 75.6, 73.6, 66.3, 39.2, 34.8, 31.1, 30.1, 27.5, 27.4, 19.6, 19.57, 12.5, 4.8; HRMS (FAB+) exact mass calc. for [M+H] ($C_{15}H_{27}O_4$) requires *m/z* 271.1909, found *m/z* 271.1914; $[\alpha]_D$ = 22.64 (c = 3.36, $CHCl_3$).

Diastereomer 4 acetonide: IR (Film): 2971, 2937, 2875, 2359, 2341, 1730, 1480, 1457, 1379, 1283, 1259, 1201, 1160, 1109, 1018, 991, 938, 901, 870 cm^{-1}; ^{1}H NMR: (300 MHz, $CDCl_3$) δ 5.03 (S, 1H), 4.90 (s, 1H), 4.21 (s, 1H), 3.97 (ddd, 2H), 3.67 (dd, 1H), 1.95 (m, 1H), 1.63 (s, 3H), 1.44 (s, 3H), 1.43 (s, 3H), 1.21 (s, 9H), 1.04 (d, 3H), 0.77 (d, 3H); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 178.8, 142.7, 110.6, 99.2, 75.8, 75.6, 66.0, 39.1, 34.6, 32.0, 30.1, 27.4, 19.6, 19.5, 14.8, 5.5; HRMS (FAB+) exact mass calc. for [M+H] ($C_{15}H_{27}O_4$) requires *m/z* 271.1909, found *m/z* 271.1891; $[\alpha]_D = 3.22$ (c = 1.0, $CHCl_3$).